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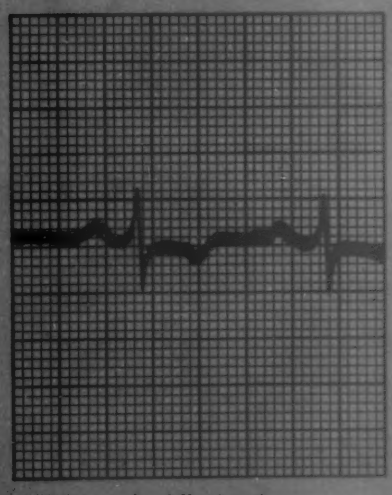
Seminar on the Role of Salt in Cardiovascular Hypertension (Part I)

MELVIN J. FREGLY, PH.D.
Guest Editor

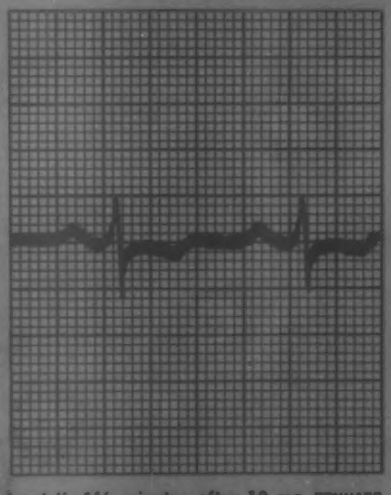
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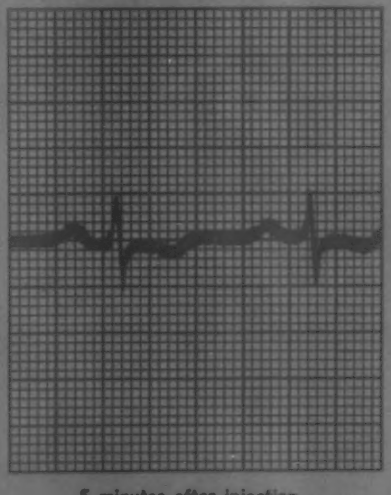
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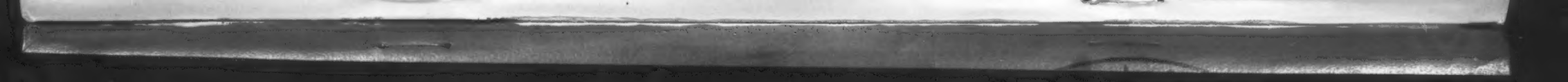


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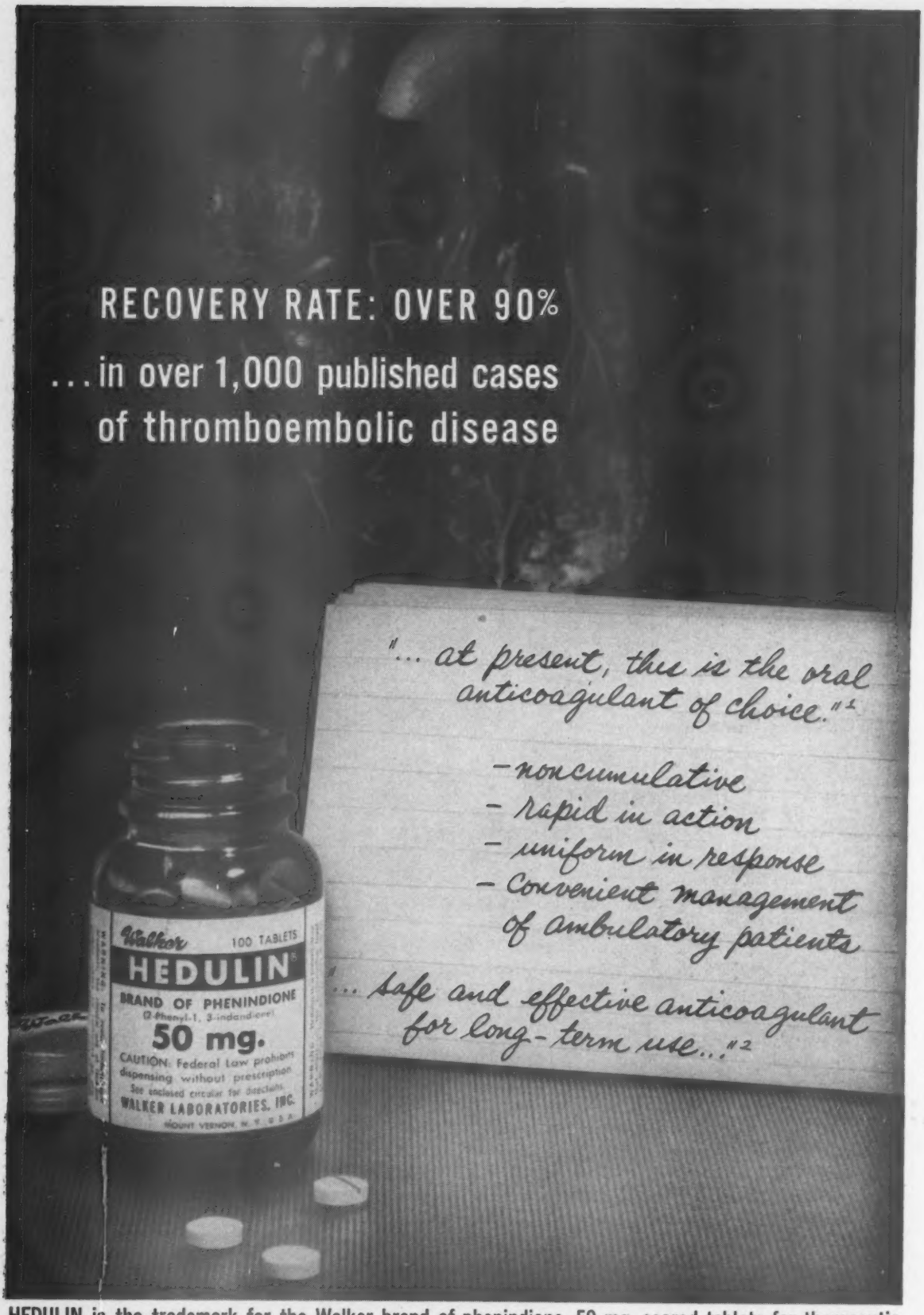
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1. Clowdus, B. F.; Higgins, J. A.; Rosevear, J. W., and Summerskill, W. H. J.: Treatment of "Refractory" Ascites with a New Aldosterone Antagonist in Patients with Cirrhosis, Proc. Staff Meet. Mayo Clin. 35:97 (March 2) 1960.

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1. Breneman, G. M., and Priest, E. McC.: Am. Heart J. 50:129 (July) 1955. 2. Tandowsky, R. M.: Am. J. Cardiol. 3:551 (April) 1959.

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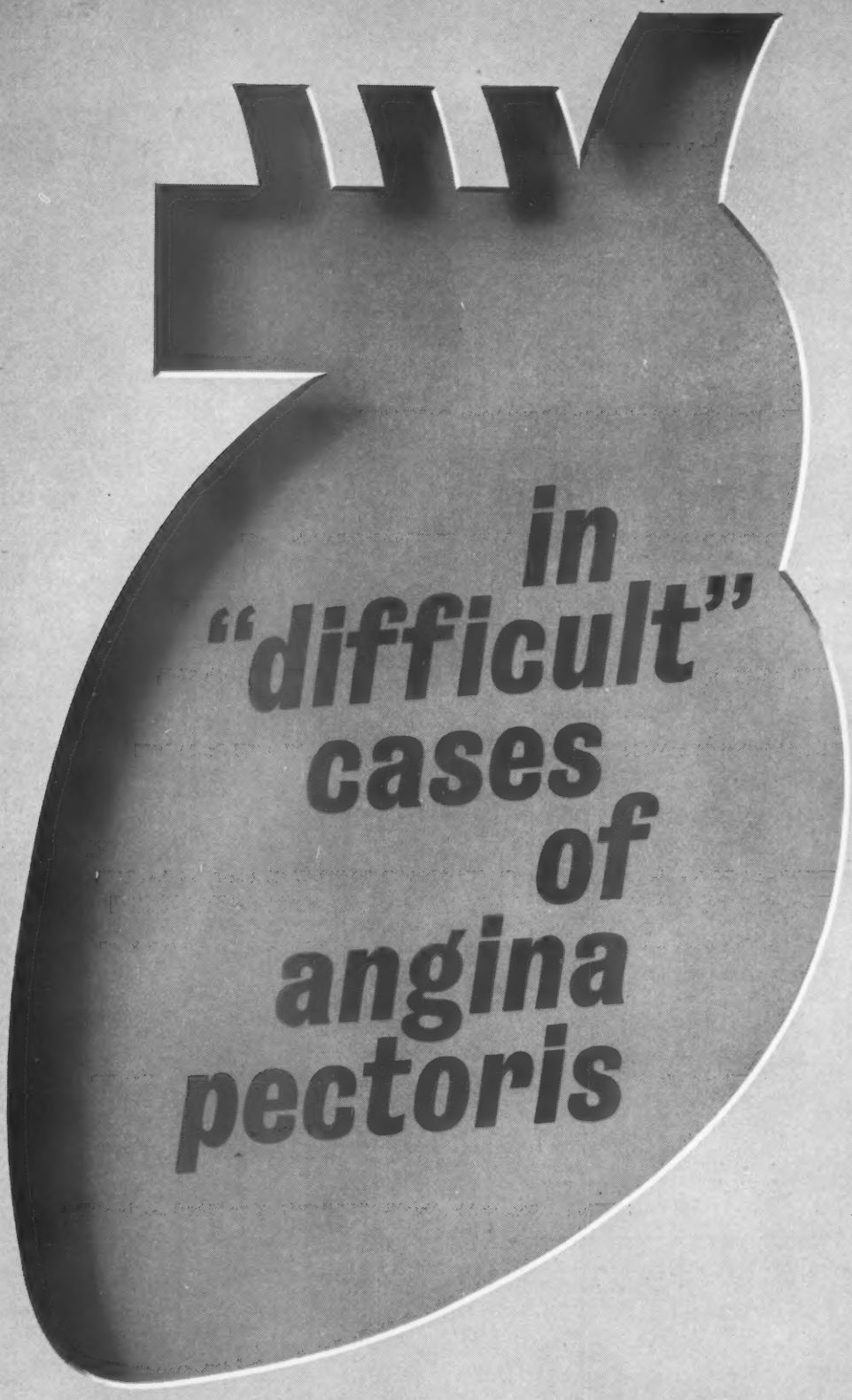
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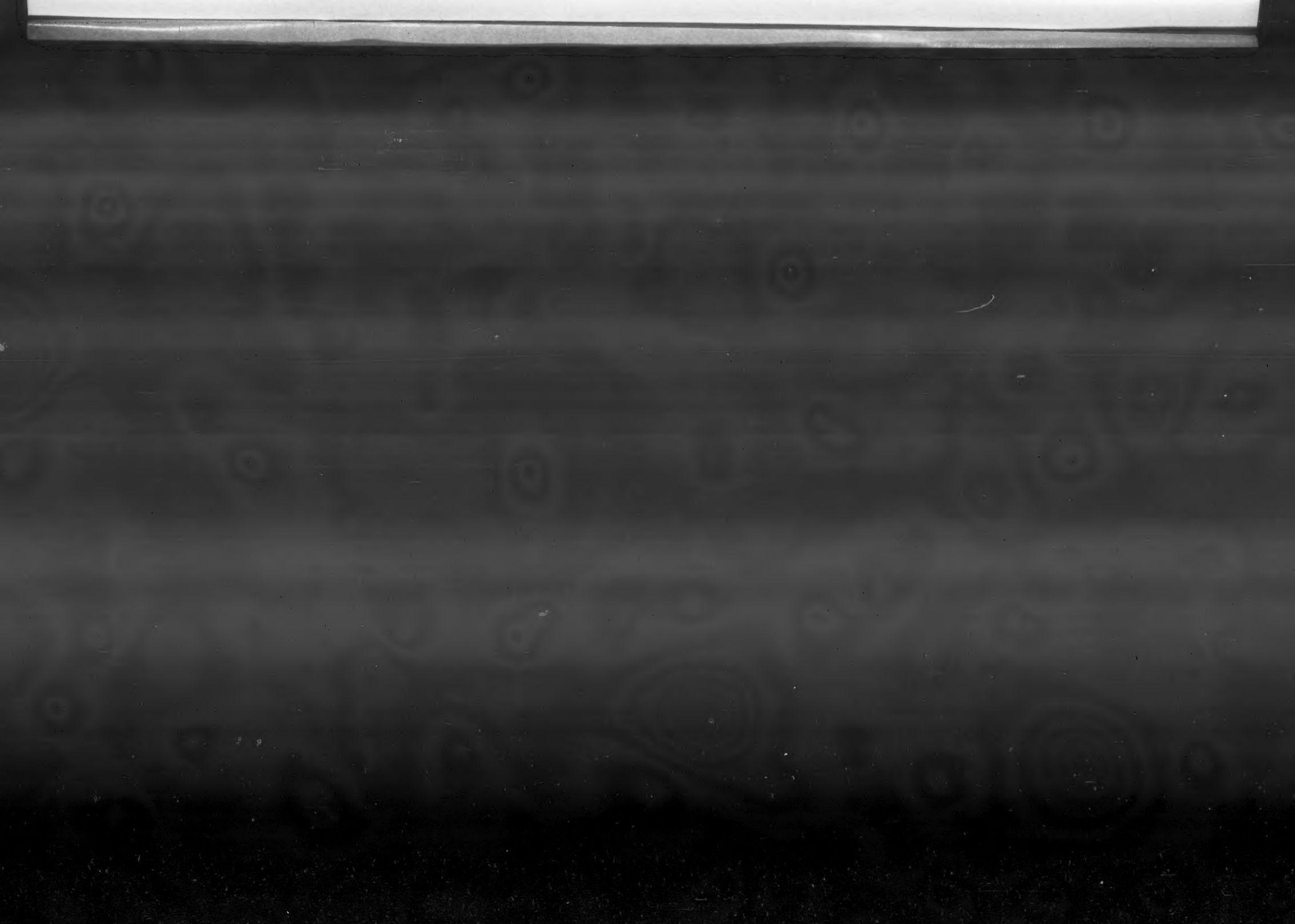
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LOUIS HORLICK

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JOHN C. OWENS, CHARLES A. ARMBRUST, JR., WILLIAM C. SUTTON, WILLIAM R. LIVESAY AND EPHRAIM L. WAGNER

The initial prolongation of the one-stage prothrombin time test following warfarin administration reflects the fall in the concentration of factor VII rather than prothrombin concentration. If danger of intravascular clotting is to be avoided early during warfarin therapy, heparin should be administered for longer periods than usual. The prothrombin concentration is a more accurate guide than prothrombin time for the dosage of the coumarin-type anticoagulants. A level of 10 to 24 per cent is recommended.

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BRUNO HORISBERGER AND SIMON RODBARD

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J. A. ABILDSKOV, ROBERT S. WILKINSON, JR., WILLIAM A. VINCENT AND WILLARD COHEN

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MYRON PRINZMETAL, HIDEO TOYOSHIMA, ALI EKMEKCI, YASUSHI MIZUNO AND TERUO NAGAYA

In this review the authors continue their study of the effect of intracellular metabolic changes on the electrogram and electrocardiogram in various grades of myocardial ischemia. The S-T elevation in severe ischemia is produced by depression of the T-Q segment and is a manifestation of negative membrane resting potential of ischemic cells due to loss of potassium ions and increase in sodium ions. On the other hand, mild ischemia is associated with cellular uptake of potassium ions and an increase in membrane resting potential, resulting in S-T depression.

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Digitalization by Combined Intravenous and Oral Administration of Two Glycosides. 504

MARCEL NEUMANN AND RAYMOND REICH

In a group of 102 patients the most effective digitalization schedule for combined therapy proved to be intravenous administration of Cedilanid-D, 0.8 mg., followed by oral digitoxin, 0.4 mg., on the same day and the following day, 0.2 mg. on the third day, and 0.1 mg. daily thereafter. Individual variations required minor adjustments in dosage.

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BERNARD H. PASTOR AND ANTHONY L. FORTE

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NANETTE KASS WENGER AND ROBERT J. PEACE

Living only several days, this premature baby showed left bundle branch block on the electrocardiogram and a rudimentary left coronary artery at autopsy.

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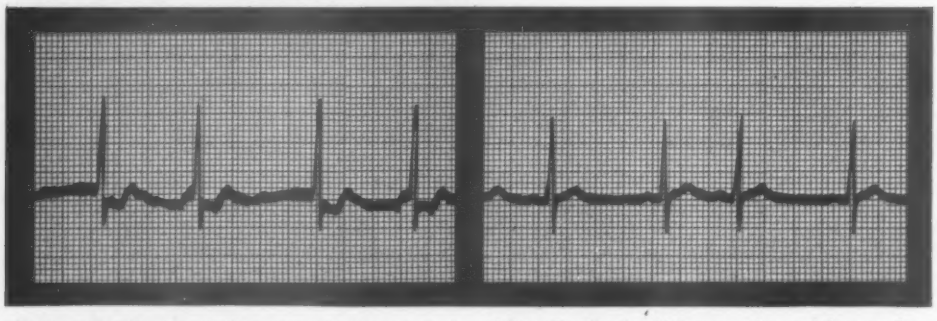
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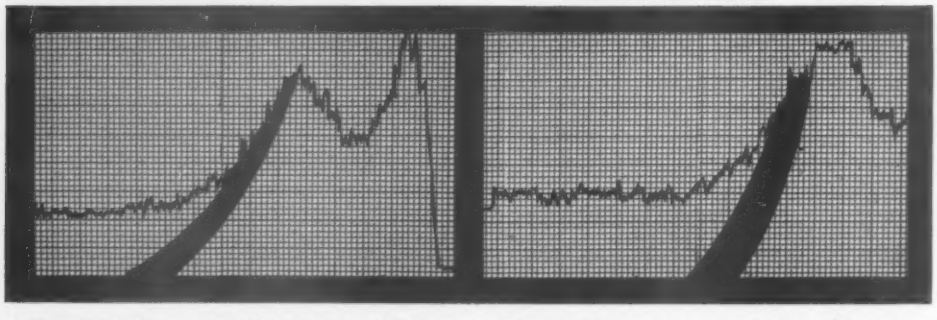


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Electrocardiographic Changes Noted at the Onset of Coronary Occlusion and Myocardial Infarction 521

LAWRENCE E. LAMB

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Seminar on the Role of Salt in Cardiovascular Hypertension (Part I)

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MELVIN J. FREGLY

Changes in Blood Pressure and Body Sodium of Rats Fed Sodium and Potassium Chloride 527

GEORGE R. MENEELY, JANET LEMLEY-STONE AND WILLIAM J. DARBY

Rats fed 9.8 per cent dietary sodium chloride revealed increased blood pressure as well as increased exchangeable and total body sodium. Addition of sufficient potassium to restore the dietary ratio of Na:K to 1 maintained significantly lower blood pressure and exchangeable body sodium. The increased body sodium in rats with normal serum sodium levels is attributed to expansion of the extracellular compartment.

Resistance to Blood Flow through the Vascular Bed of the Dog Forelimb. Local Effects of Sodium, Potassium, Calcium, Magnesium, Acetate, Hypertonicity and Hypotonicity. 533

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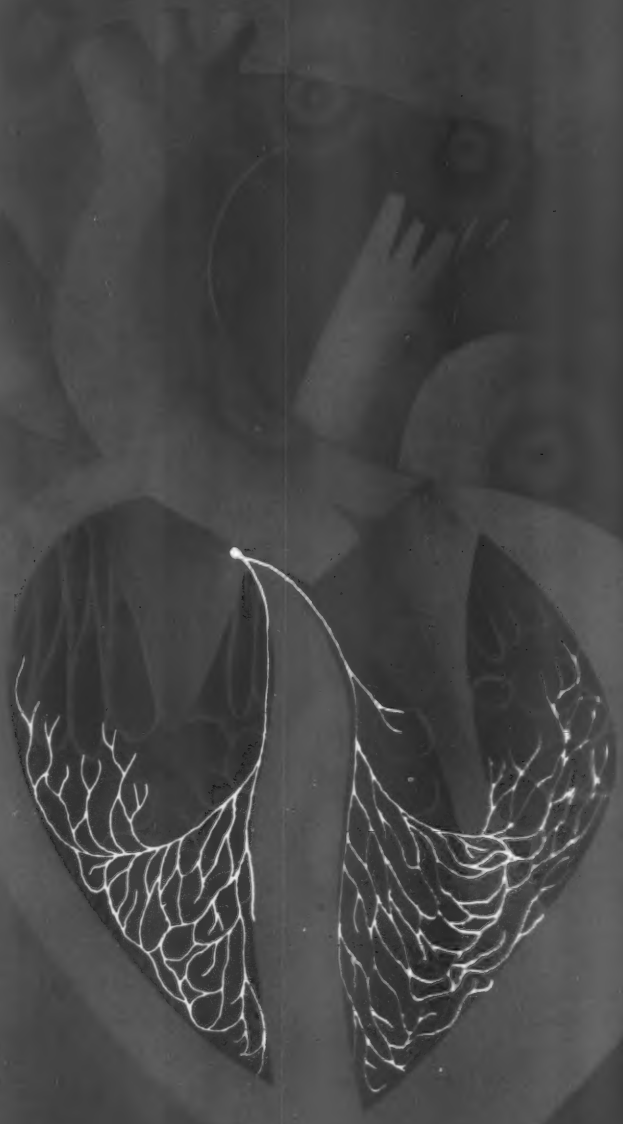
In the foreleg of the dog increased blood tonicity or slight elevation in the blood concentration of potassium, magnesium or acetate produces arteriolar dilation. Decreased tonicity or slight elevation of calcium concentration produces active arteriolar constriction. Changes in sodium concentration exert little effect except through changes in blood tonicity.

Effect of Hypertension and Sodium Chloride on Vascular Reactivity in Vitro . . 542

SAMUEL MALLOV

In hypertensive rats the arterial walls become structurally and functionally altered. The functional alterations include a decreased reactivity to catecholamines and a changed contractile behavior in the presence of elevated sodium ion concentrations and/or hypertonic solutions.

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Role of Electrolytes in the Contractile Machinery of Vascular Smooth Muscle . . 549

DAVID F. BOHR AND PATRICIA L. GOULET

This paper discusses the responsibility of the altered functional electrolyte composition in vascular smooth muscle for the exaggerated muscular response to normal vasoconstrictor stimuli. Potassium influences this response through its cellular membrane gradient and directly by its intracellular concentration. Decreased sodium concentration increased responsiveness of smooth muscle while lowered calcium levels decreased it.

A Closer Look at the Problem of Vascular Reactivity of Isolated Aortic Strips . . 557

DAVID B. GORDON AND ALFRED T. NOGUEIRA

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LEWIS K. DAHL

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SIMON KOLETSKY

Although chronic ingestion of salt produces hypertensive cardiovascular renal disease in the rat resembling that in man, the morphologic lesions in both are not strictly comparable. Renal ablation in the rat enhances the role of salt loading in hypertensive vascular disease, possibly through defective metabolism of sodium.

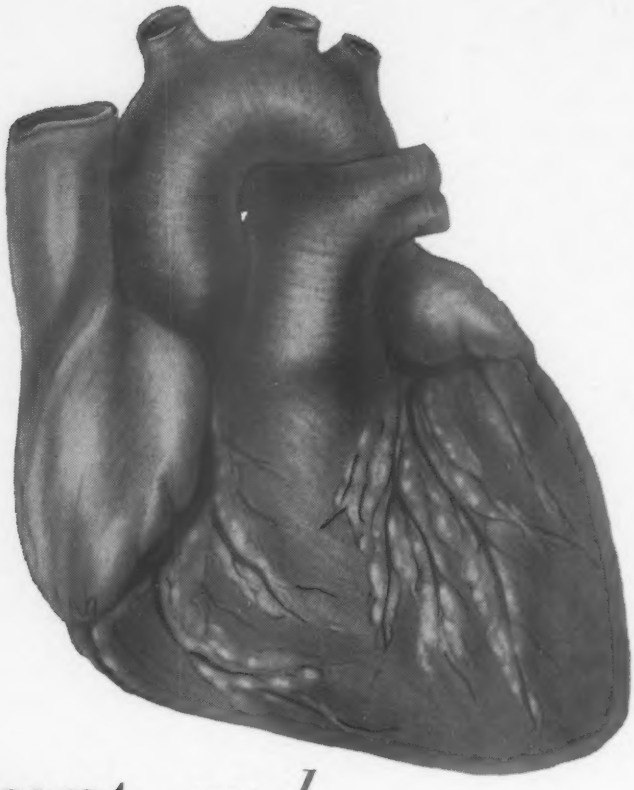
Hypertension and Renal Cardiovascular Pathology in Adrenalectomized Salt-Loaded Rats 582

GEORGE F. WILGRAM AND DWIGHT J. INGLE

Experiments in rats reveal that salt-loading induces hypertension and early nephrosclerosis, even in the absence of the adrenal glands. Mineralosteroids of the adrenal cortex apparently merely potentiate the primary damaging effect of a high salt load, but are not themselves the primary pathogenic agents.

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The Role of Salt in Health and Disease 593

ARTHUR GROLLMAN

Dr. Grollman reviews the physiologic role of salt in maintenance of a normal fluid volume and acid-base balance and the role of abnormal sodium metabolism in congestive heart failure, renal disease and hypertension. Despite the availability of potent saluretic agents, he believes that dietary sodium restriction still constitutes an important procedure in the treatment of edema and hypertension.

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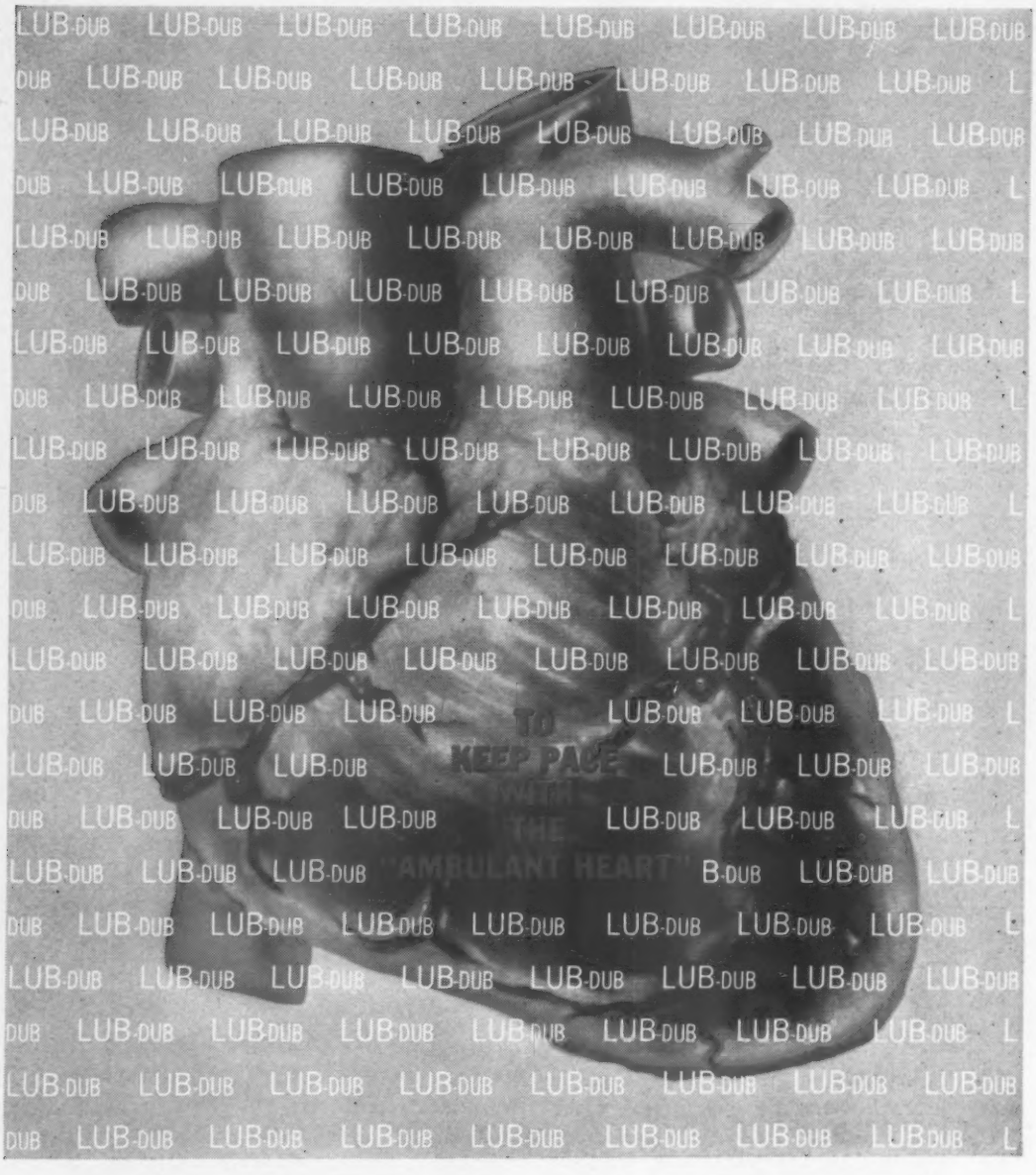
The Eleventh Annual Convention of the College will be held in Denver, Colorado at the Denver Hilton, May 29 to June 2, 1962.

Abstracts of papers intended for the scientific program should be sent before January 1, 1962 to Dr. James E. Crockett, Department of Medicine, University of Kansas Medical Center, Kansas City, Kansas. Abstracts should be approximately 250 words in length. Original and three copies are to be supplied.

Commercial exhibitors should write to Dr. Philip Reichert, Executive Director of the College, Empire State Building, New York 1, New York. Journal advertisers will have point priority in the assignment of exhibit space.

Abstracts of scientific exhibits should also be sent to the office of the Executive Director.

Index to Advertisers on pages 67 and 68



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"...the electrocardiogram [taken] during exercise is an extremely valuable adjunct in the detection of myocardial disease..."

Bellet, S., Deliyiannis, S. and Eliakim, M.: Am. J. Cardiol. *8*:385 (Sept.) 1961



The electrocardiogram during exercise has now become a practical procedure with the introduction of *RKG 100*, the radio-electrocardiograph. The *RKG 100* eliminates all connective cables between patient and apparatus and permits unrestricted recording of the EKG while subjects are exercising or undergoing the physical and emotional stress of everyday activity. It has been used successfully with more than 1,200 patients who were performing mild (Master Two-Step Test) or strenuous (stationary bicycle) exercise. Significantly in one clinical study conducted with this new instrument, it was reported that "... 58% of our cases with cardiac disease showed changes only or chiefly during exercise."[1]

References: 1. Bellet, S., Deliyiannis, S. and Eliakim, M.: Am. J. Cardiol. *8*:385 (Sept.) 1961. Bellet, S., Deliyiannis, S. and Eliakim, M.: Circulation (in press)

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REFERENCES: **1.** Ellis, L. B. *et al.:* Circulation *17*:945, May 1958. **2.** Friedlander, H. S.: Am. J. Cardiol. *1*:395, Mar. 1958. **3.** Riseman, J.E.F.: New England J. Med. *261*:1017, Nov. 12, 1959. **4.** Russek, H. I. *et al.:* Circulation *12*:169, Aug. 1955. **5.** Russek, H. I.: Am. J. Cardiol. *3*:547, April 1959. **6.** Tortora, A. R.: Delaware M. J. *30*:298, Oct. 1958. **7.** Waldman, S. and Pelner, L.: Am. Pract. & Digest Treat. *8*:1075, July 1957.

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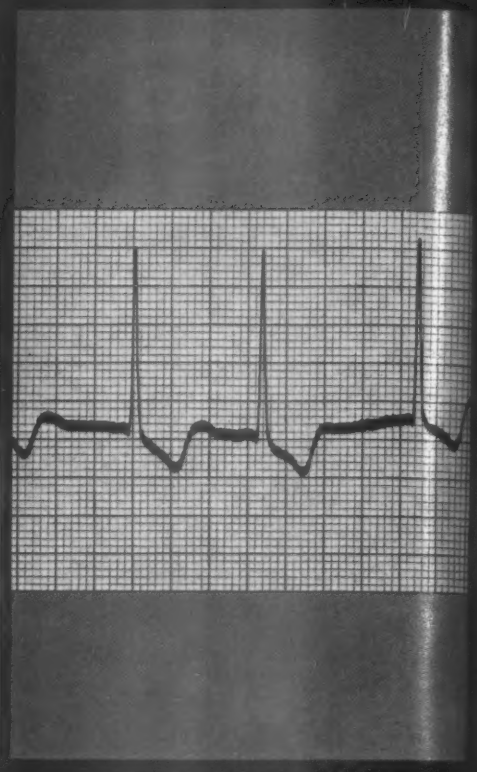
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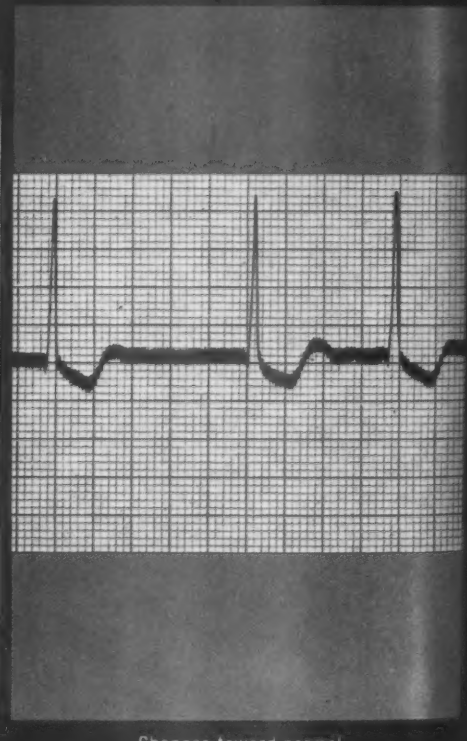


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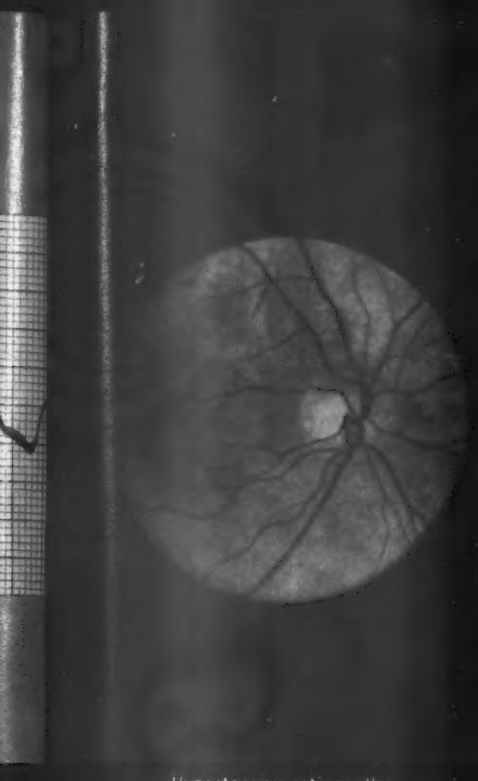
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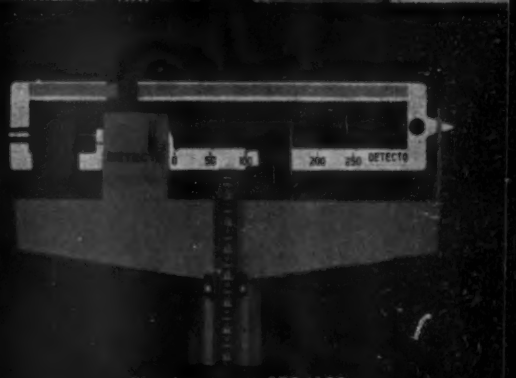


Hypertensive retinopathy with hemorrhages.

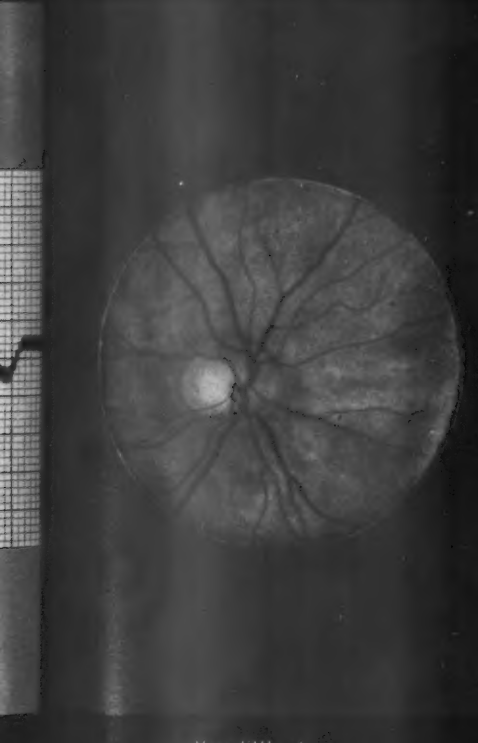


Liver palpable 5 fingerbreadths below costal margin.

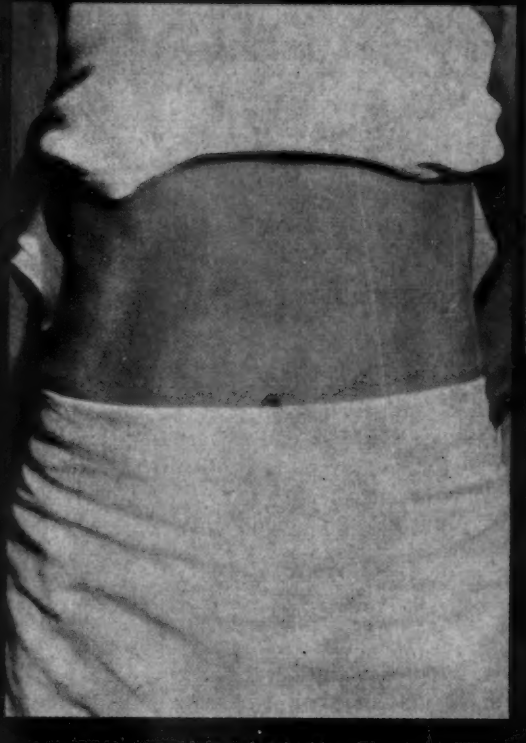




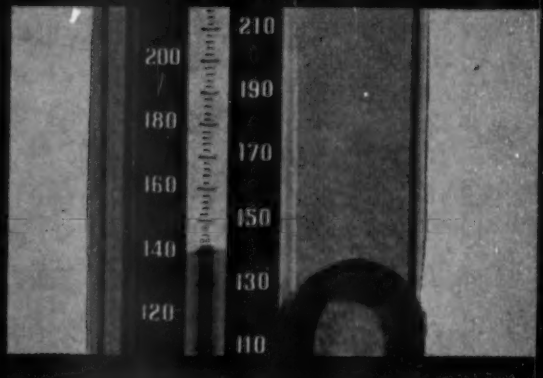
Blood pressure 270/120.
Weight 110½ pounds.

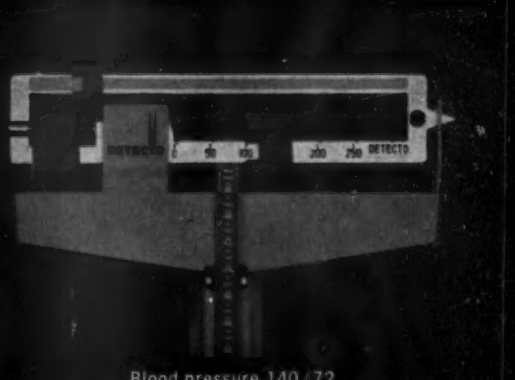


Very little change.



Liver not palpable.





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For patients suffering from tension/anxiety states, we are offering the medical profession Listica— a new and selectively different monocarbamate. Frankly, we would be hesitant about entering a field already crowded with good drugs were it not for the marked differences Listica presents.

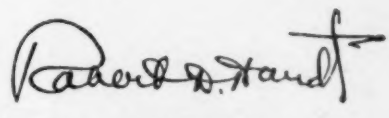
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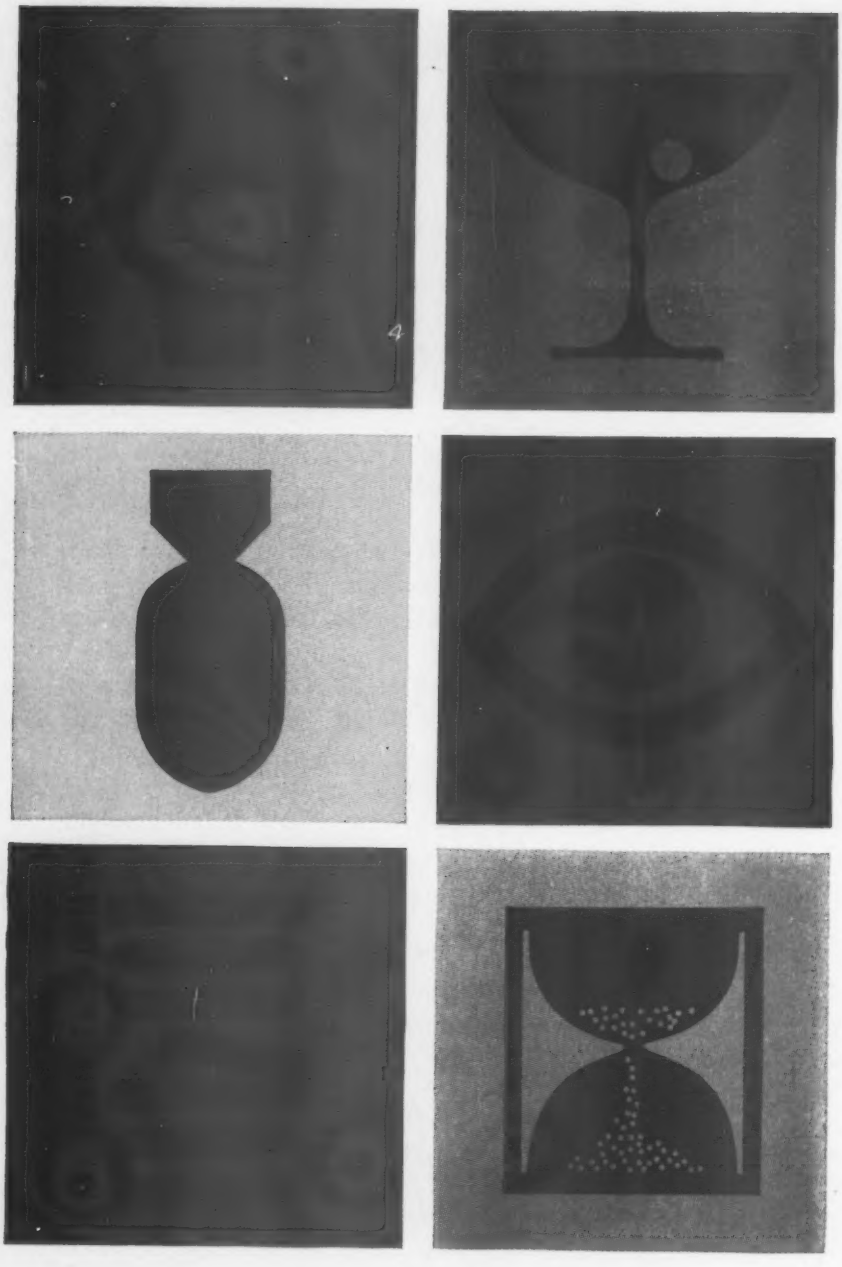
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without known toxicity or contraindications Listica is safe, as well as effective. Chronic studies[14] in rats (12 months) and dogs (6 months) were free of toxic manifestations at oral dosage levels as high as 200 mg./kg./day (approximately 10 times the recommended human dosage). No macroscopic or microscopic changes in tissues, organs or blood indicative of toxicity were observed, even at doses up to 320 mg./kg. In humans, there have been no adverse blood, urine or cardiac changes; liver profiles were negative, and jaundice has not been noted.

without serious side effects or habituation During three and one-half years of clinical study in 1,759 patients,[2-13] Listica has produced no serious side effects. Less than 4% of patients experienced any side effects, and these were invariably minor and transient. Most frequent (38 cases) was mild drowsiness, which disappeared after the first few days of Listica therapy. Habituation, cumulative effects, or withdrawal symptoms have not been noted, even in patients taking Listica as long as two years.

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References:

[1]Bastian, J. W.: Classification of CNS Drugs by a Mouse Screening Battery. To be published in Intern. Arch. de Pharmacodynamie; [2]Hubata, J. A., and Hecht, R. A.: Review of Clinical Use of Hydroxyphenamate (Listica) in 1,759 Patients. To be published in Clinical Medicine; [3]Taub, S. J.: Management of Anxiety in Allergic Disorders—New Approach. To be published in Psychosomatics; [4]Cahn, B.: Experience with a New Tranquilizing Agent (Hydroxyphenamate). *Ibid;* [5]Alexander, L.: Effect of Hydroxyphenamate on Conditional Psychogalvanic Reflex in Man. Supplement to Diseases of the Nervous System, Sept., 1961; [6]Cahn, B.: Effect of Hydroxyphenamate in Treatment of Mild and Moderate Anxiety States. *Ibid;* [7]Cahn, M. M., and Levy, E. J.: Use of Hydroxyphenamate (Listica) in Dermatological Therapy. *Ibid;* [8]Davis, O. F.: On Use of Hydroxyphenamate in Anxiety Associated with Somatic Disease. *Ibid;* [9]Eisenberg, B. C.: Amelioration of Allergic Symptoms with a New Tranquilizer Drug (Listica). *Ibid;* [10]Friedman, A. P.: Pharmacological Approach to Treatment of Headache. *Ibid;* [11]Greenspan, E. B.: Use of Hydroxyphenamate in Some Forms of Cardiovascular Disease. *Ibid;* [12]Lunde, F., Davis, J., and Gouldmann, C.: Clinical Trial of Hydroxyphenamate in Alcoholic Patients. *Ibid;* [13]McLaughlin, B. E., Harris, J., and Ryan, F.: Double Blind Study Involving "Listica," Chlordiazepoxide, and "Placebo" as Adjunct to Supportive Psychotherapy in Psychiatric Clinic. *Ibid;* [14]Bastian, J. W.: Pharmacology and Toxicology of Hydroxyphenamate. *Ibid;* [15]Bossinger, C. D.: Chemistry of Hydroxyphenamate. *Ibid.*

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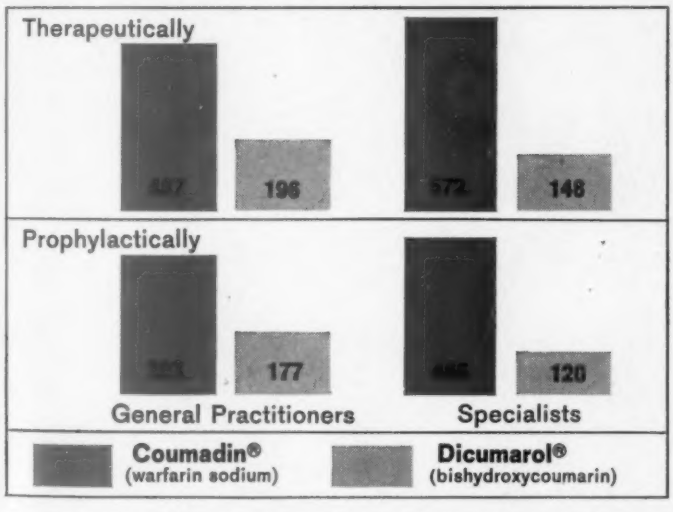
No. 2 of a series reporting on Endo Laboratories' Anticoagulant Survey

Nationwide Survey Explores Current Use of Anticoagulants in Angina Pectoris

In the first of this series of reports on the current application of oral anticoagulants in daily practice, data based on replies from 10,016 physicians showed that these agents were being widely used in *long-term therapy of myocardial infarction.*

Since the anginal syndrome may be the herald of coronary thrombosis and myocardial infarction, it is of interest to note whether anticoagulants are being employed therapeutically and prophylactically in patients with angina.

The following graph, based on Endo Laboratories' *Anticoagulant Survey*, demonstrates the extent to which anticoagulation is used in *angina pectoris* among 3,092 general practitioners and 2,626 specialists prescribing Coumadin® most often, as compared to 1,689 general practitioners and 804 specialists using Dicumarol.®



Physicians Treating Angina Pectoris with Oral Anticoagulants—Therapeutically and Prophylactically

While the use of anticoagulants in angina pectoris was higher among specialists than among general practitioners, both used Coumadin® more frequently than Dicumarol.® Tabulation[1] of all replies to *Anticoagulant Survey* has shown that 61.4 per cent of responding physicians prescribed Coumadin® most often, as compared to 27.6 per cent who prescribed Dicumarol,® the *second* most frequently specified oral anticoagulant—a ratio of more than 2:1.

Anticoagulants Widely Used in Coronary Artery Disease

Because of the relationship of the anginal syndrome to *coronary atherosclerosis, coronary insufficiency,* and *impending myocardial infarction,* it is also interesting to note the percentage of physicians who reported their use of anticoagulants in *these* conditions.[1]

Indication	All Anticoagulants: Therapeutically	All Anticoagulants: Prophylactically
Coronary Atherosclerosis	11.3%	10.2%
Coronary Insufficiency	29.2%	23.8%
Impending Myocardial Infarction	52.5%	39.9%

Percentage of Physicians Using Anticoagulants in Other Coronary Artery Disease

Anticoagulant Therapy May Prevent First Myocardial Infarction

The findings of *Anticoagulant Survey* are consonant with recently reported clinical experience demonstrating the value of long-term anticoagulation in angina pectoris. For example, on the basis of his results in general office practice, Nora[2] believes that *"long-term anticoagulation therapy not only reduces the probability of myocardial infarction in patients having sustained previous infarctions but is effective in preventing a first infarction in patients with angina."* The drug used by Nora was Coumadin.

"The most significant advantage is the great ease in maintaining patients in a therapeutic range. It has been rewarding to find, month after month, patients varying no more than three or four seconds in their prothrombin times on their established dosage of [Coumadin]."[2]

1. Littman, M. L.; Barrett, E. A., and Shapiro, S.: Scientific Exhibit, 110th Annual Meet., A.M.A., New York, N. Y., June 25-30, 1961. 2. Nora, J. J.: M. Times 89:502, May, 1961; idem: J.A.M.A. 174:118, Sept. 10, 1960.

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INJECTION

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"...A strong pressor effect with a myocardial-stimulating action in experimental studies."[1] "...Tens of thousands of intramuscular and subcutaneous injections. ... Not a single instance of tissue injury was observed."[2]

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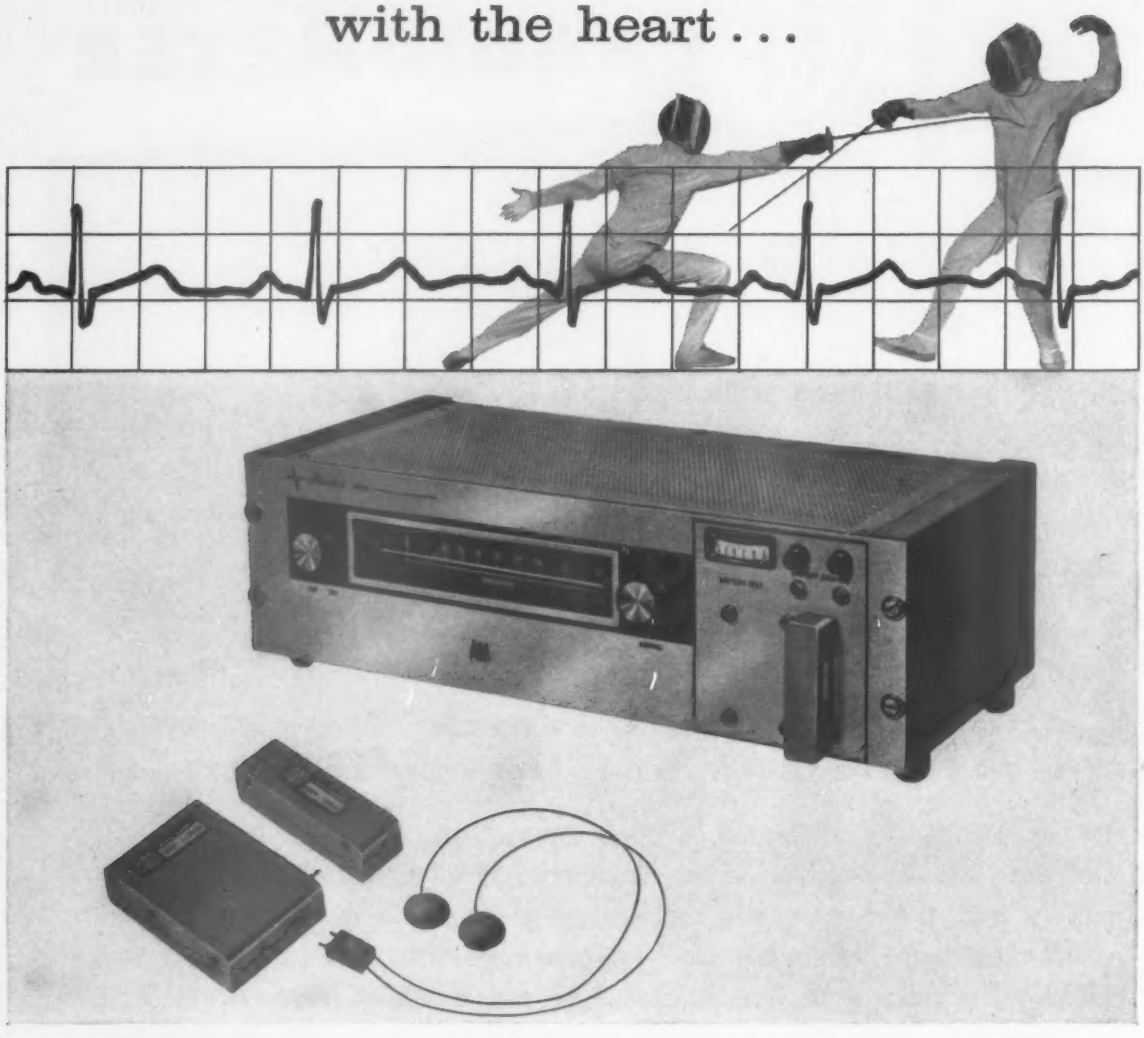
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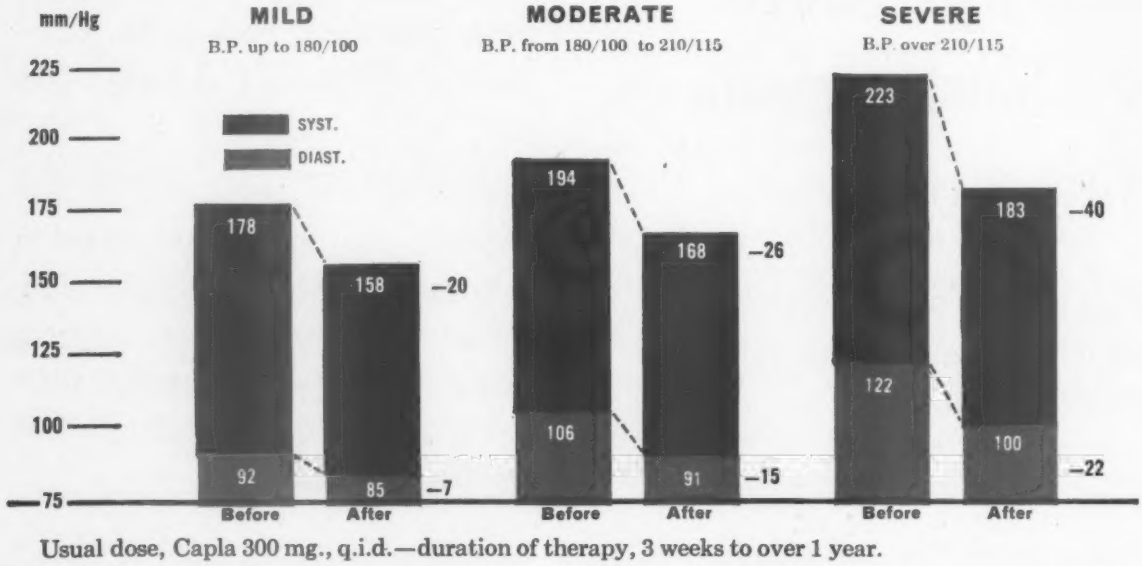
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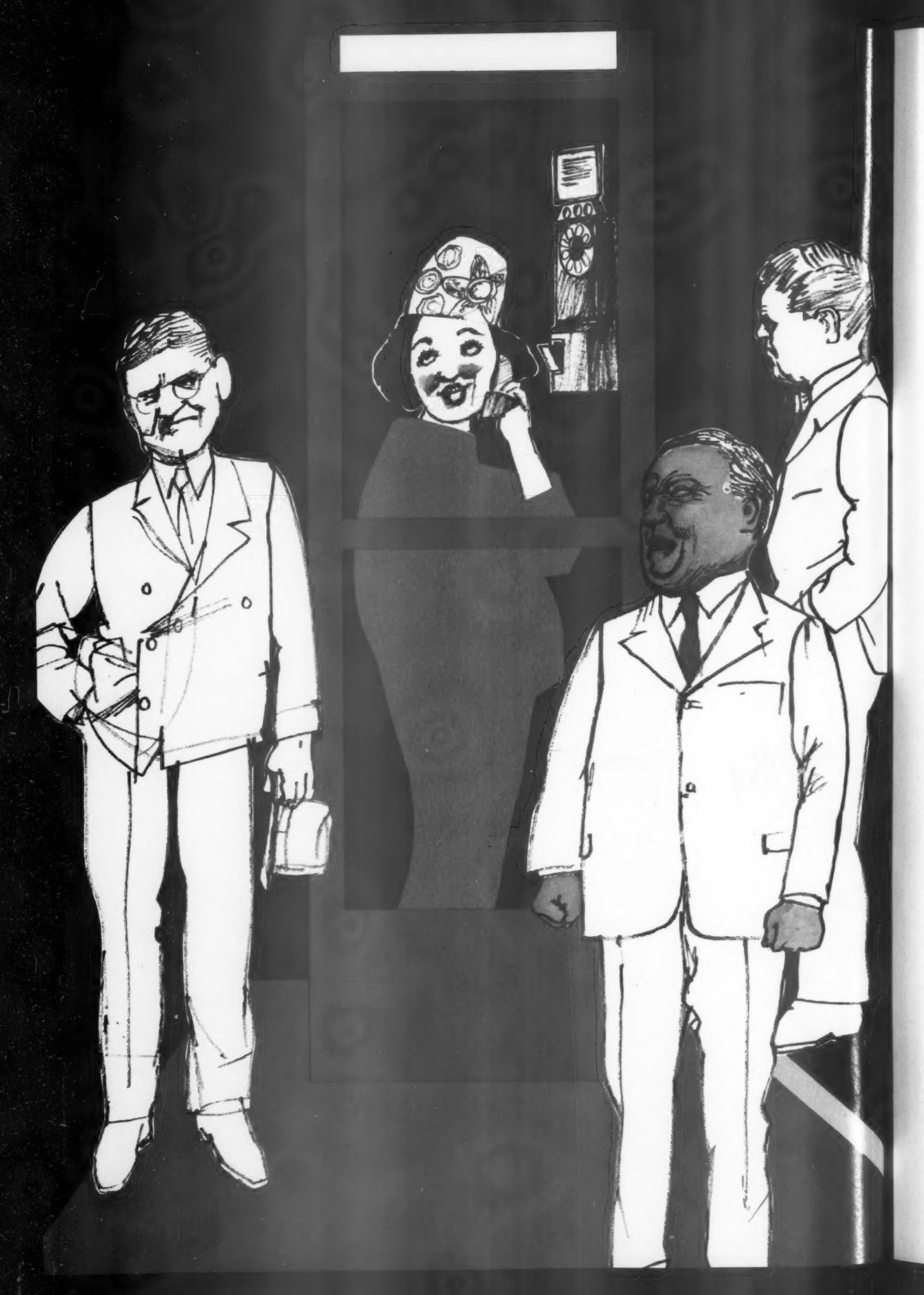
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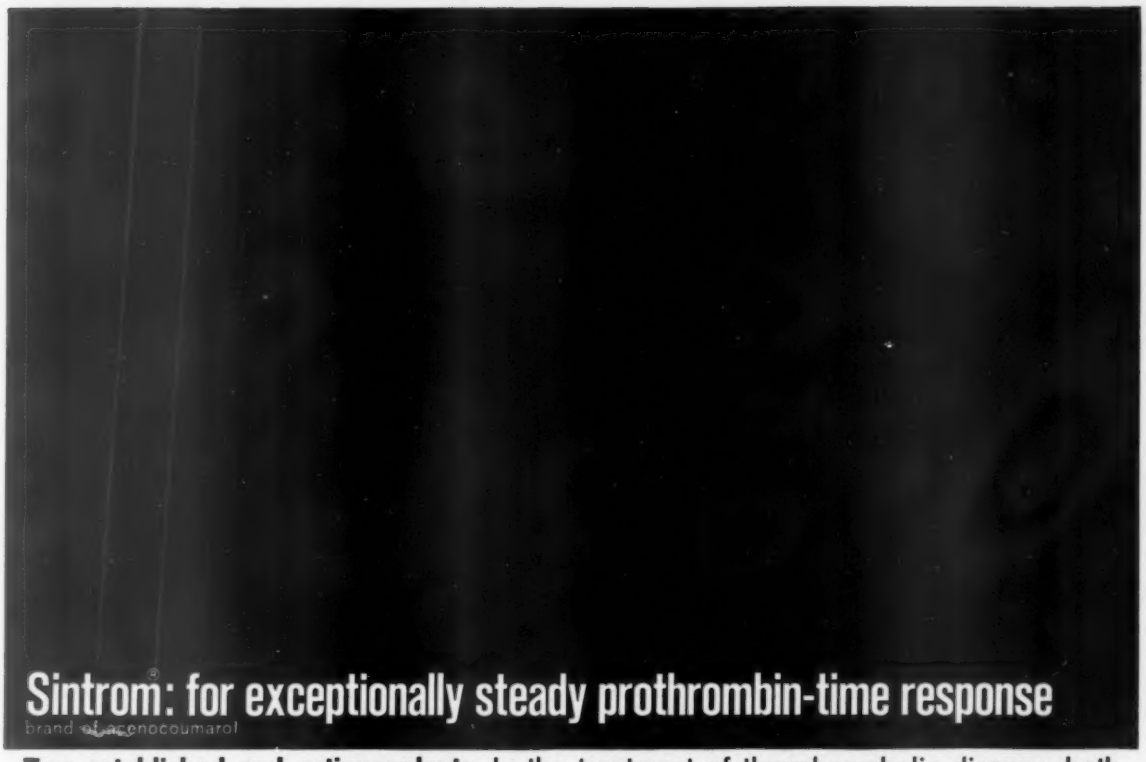
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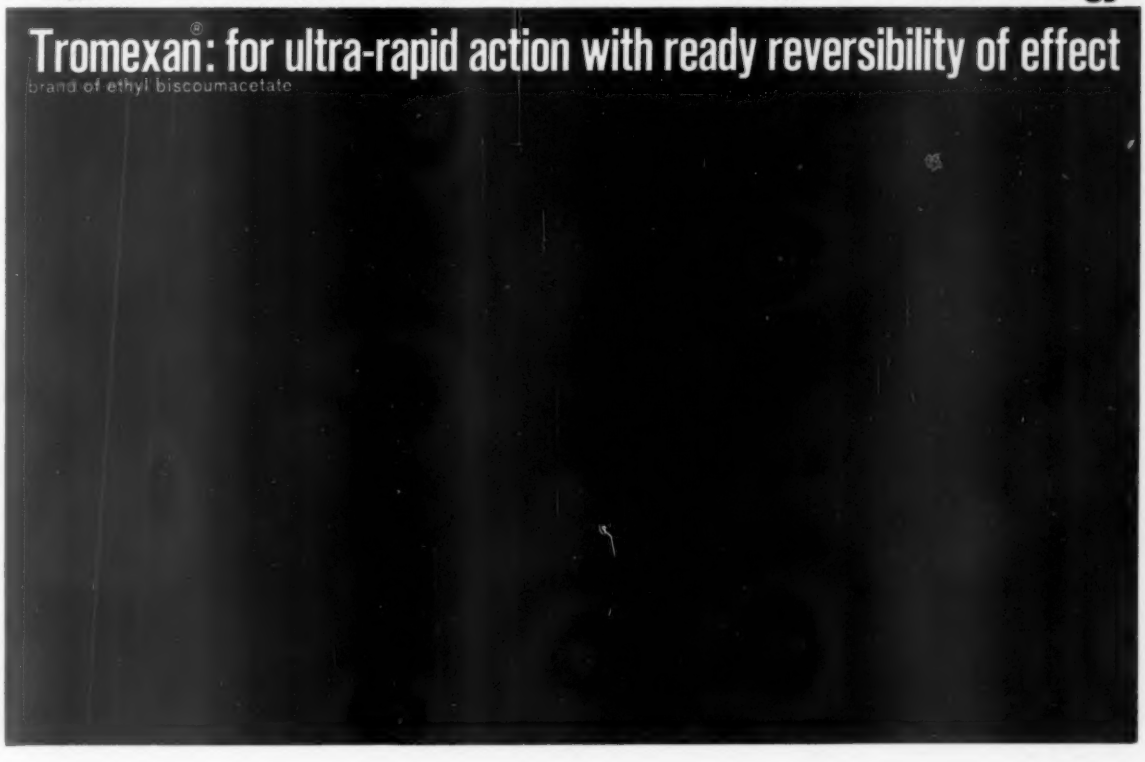
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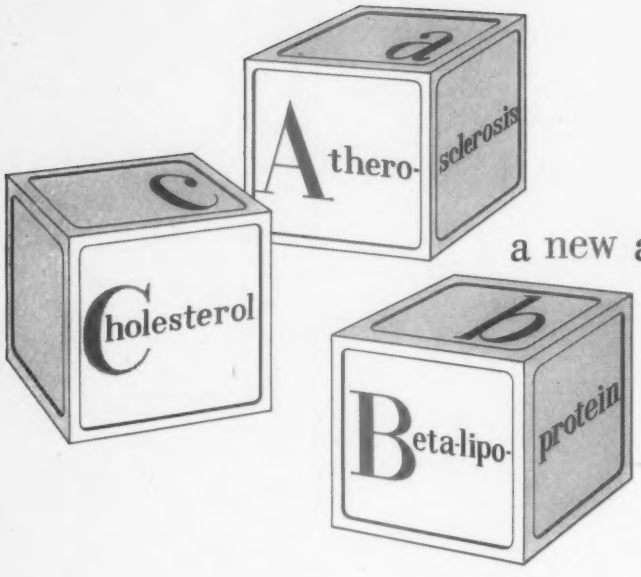
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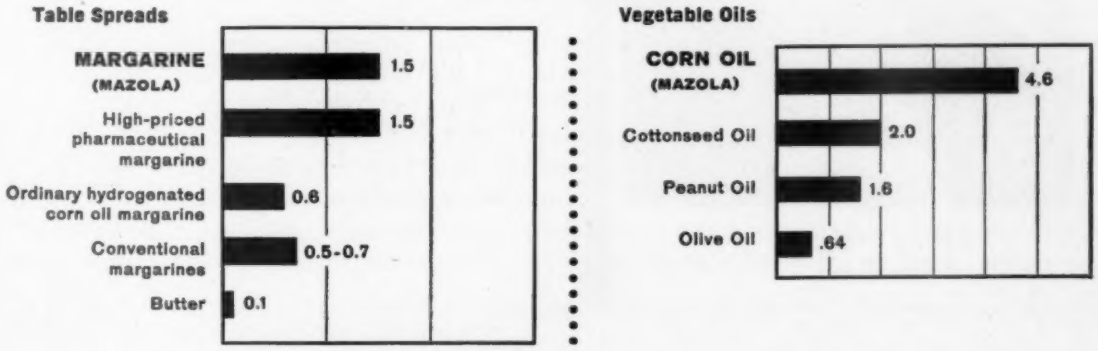


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Monounsaturated	40	23	32	9
Saturated	14	8	11	3
Natural Sitosterols	0.5	0.3	1	0.3
Natural Tocopherols	0.08	0.045	0.08	0.020
Cholesterol	none	none	none	none
Sodium	0.9	0.5	none	none

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The American Journal of Cardiology

VOLUME VIII OCTOBER 1961 NUMBER 4

Clinical Studies

Platelet Adhesiveness in Normal Persons and Subjects with Atherosclerosis

Effect of High Fat Meals and Anticoagulants on the Adhesive Index*

LOUIS HORLICK, M.D., F.R.C.P.(C)

Saskatoon, Canada

DUGUID[1] HAS FOCUSED ATTENTION on von Rokitansky's original suggestion that atheroma is produced by the deposition of "an endogenous product derived from the blood and for the most part from the fibrin of the arterial blood." In a pathologic study of coronary thrombosis, Duguid has described the transformation of thrombi into atheroma, the fibrin being transformed into fibrous tissue and the red cells and platelets into the fatty "gruel" of the classical atheroma, the whole covered by a layer of endothelium. The episodic deposition of fibrin, red cells and platelets would presumably account for the growth of the atheroma and encroachment on the vessel lumen.

This theory has received support from studies reporting increased coagulability of the blood in ischemic heart disease.[2–10] McDonald and Edgill[9] noted a statistically significant difference between patients with ischemic heart disease and controls in respect to thromboplastin generation, platelet stickiness, fibrinogen estimation and prothrombin time. They conceded, however, that since tissue destruction is known to be followed by increased coagulability of the blood it was entirely possible that hypercoagulability might be a result rather than a cause of ischemic heart disease. In a later study[10] they demonstrated that the change in coagulability tended to be phasic rather than constant with periodic swings from normal levels to a state of hypercoagulability. Duguid's theory did not take into account the relationship of dietary fat to atherogenesis. During the past few years several studies[11–15] have suggested that dietary fat enhances coagulability and have provided a connecting link between alimentary lipemia and the thrombogenic theory of atherogenesis. Mustard[14] studied the response to a meal rich in animal fats in atherosclerotic patients and in normal subjects with and without a family history of atherosclerosis. The atherosclerotic individuals had the greatest mean increase in plasma density and Christmas factor activity and a decrease in antihemophilic globulin activity. The normals with no family history of atherosclerosis showed the least change in these indices. The normals with a positive family history had about the same degree of change as did the group with clinical complications of atherosclerosis. In both of these groups the

* From the Department of Medicine, University of Saskatchewan, Saskatoon, Canada. This work was supported by a grant from the National Research Council (Canada).

TABLE I

Effect of Passage through the Fiberglas Filter on a Red Cell Count of Reconstituted Platelet-Poor Citrated Blood

Subject	Prefiltration			Postfiltration		
	Red Blood Cell Count	Platelet Count	Ratio Red Blood Cell/Platelets	Red Blood Cell Count*	Platelet Count*	Ratio Red Blood Cell/Platelets
A. L.	4,770,000	48,000	99.8	4,940,000	32,000	155.9
R. M.	4,840,000	37,000	132.1	4,710,000	30,000	161.5
F. S.	4,920,000	64,000	76.4	5,040,000	45,000	113.1
C. W.	4,670,000	44,000	105.0	4,650,000	41,000	112.0
R. H.	4,860,000	67,000	72.8	5,030,000	51,000	98.3

* Corrected for dilution.

platelet count was more reduced and the prothrombin time shorter than in the group with the negative family and personal histories. Mustard's observations suggest an important causal role for hypercoagulability in atherogenesis.

Since platelets are known to play a key role in intrinsic clotting mechanisms, we decided to study platelet adhesiveness in normal individuals and in those with atherosclerosis. Observations were also made on the effects of high fat meals and anticoagulants on platelet adhesiveness.

MATERIALS AND METHODS

Our subjects were normal, healthy students and hospital personnel and patients with clinical manifestations of arteriosclerosis of the coronary or peripheral vessels or both. Platelet adhesiveness was measured by Moolten and Vroman's method.[16]

Venous blood was drawn into citrated siliconized syringes and platelet and red cell counts were done. Procaine was used as a diluent for the platelet counts which were made with a phase microscope and special thin counting chambers.[17] An aliquot of blood was then passed through a specially prepared Fiberglas filter and washed through with saline. Counts were made on the filtrate. The ratio of red cells to platelets was determined from the counts made before and after filtration. Dividing the ratio after filtration by the ratio before filtration yielded the "adhesive index." All blood samples were filtered within ten minutes of being drawn. Serum cholesterol was determined by Abell's method[18] and serum triglycerides by Van Handel and Zilversmit's method.[19]

CRITIQUE OF THE METHOD

In their original report Moolten and Vroman[16] stated that red cell stickiness was negligible and did not influence the adhesive index appreciably. However, no specific data were published to support this statement. Our own experience suggested that red cells were often left behind in the filter after the saline washings. The use of a ratio of red cells to platelets might compensate for differences in filter sizes, and hence for differences in dilution of the filtrate, but could not eliminate the possibility of differential stickiness of red cells or platelets.

In an effort to clarify this matter further, a study was carried out. Citrated blood was spun at low speed (1,000 r.p.m. for 15 minutes) to separate the red cells and the platelet-rich plasma. The latter was then centrifuged at high speed (4,000 r.p.m. for 30 minutes) in a refrigerated centrifuge to precipitate the platelets, and the platelet-poor plasma drawn off. The red cells were then resuspended in platelet-poor plasma. Red cells and platelet counts were made before and after filtration (through the Fiberglas filter) (Table I). There were no significant changes in either platelets or red cells after filtration. This would support Moolten and Vroman's statement that red cells are not retained in the filter in significant numbers. The fact that few platelets were retained would also suggest that the "sticky platelets" are retained in the filter, not the nonsticky ones surviving high speed centrifugation.

Finally, we compared the results obtained by Moolten and Vroman's technic with those obtained by the Wright rotating glass drum technic.[20] In the latter method an aliquot of citrated blood is rotated at constant speed in a glass drum, and platelet counts are made at regular intervals (30, 60 and 90 minutes). The sticky platelets presumably adhere to the glass and there is no significant adhesion of red cells to the glass. In sixteen normal subjects in whom a comparison was made between adhesive index and per cent retention of platelets at 30, 60 and 90 minutes, no significant correlation could be seen (Table II).

TABLE II
Comparison of Adhesive-Index Values with Retention of Platelets in Wright's Rotating Glass Drum in Normal Subjects

Subject	Age (yr.)	Adhesive Index	Per Cent Retention of Platelets in Rotating Drum		
			30 Min.	60 Min.	90 Min.
A. L.	50	1.07	26.4	45.2	60.4
R. M.	63	1.04	14.2	26.8	35.4
F. S.	62	1.12	37.4	46.6	59.2
C. W.	63	1.19	33.2	42.7	54.9
R. H.	48	1.01	34.1	63.2	64.8
H. P.	59	1.00	27.5	43.5	49.5
E. R.	62	1.08	49.2	55.4	57.9
G. L.	56	0.98	36.7	39.4	41.8
W. L.	75	1.08	10.5	15.7	21.5
G. P.	58	1.14	41.0	59.9	63.9
T. R.	54	1.15	5.3	12.2	28.7
R. C.	73	1.15	36.1	46.8	59.7
B. S.	53	1.19	37.4	59.4	67.7
P. L.	62	1.02	28.3	36.7	44.7
A. M.	51	1.05	28.4	43.2	51.2
C. P.	52	1.00	55.1	69.5	73.3

This suggests that the Wright technic and the Moolten and Vroman technic measure different aspects of platelet behavior. Roskam et al.[21] have studied the behavior of moderately citrated blood when rotated in Wright's rotator. They concluded that adhesion of platelets to the tube of the rotator had something to do with clotting processes in their plasmatic atmosphere. The plasmatic atmosphere has been shown to contain calcium, albumin, alpha, beta and gamma globulins, fibrinogen, prothrombin, proaccelerin, proconvertin (antihemophilic globulin), Christmas factor, Stuart Prower factors and perhaps also antifibrinolysin. The prolonged period of rotation of the blood in Wright's method is known to wash the calcium out of the plasmatic atmosphere and render some platelets nonadhesive. Adhesiveness can be restored by washing the platelets in saline and suspending them in saline to which calcium chloride has been added for 24 hours at 4°C. Moolten and Vroman's method involves only a brief contact of citrated blood and glass, and the subsequent washing with saline is not likely to modify the plasmatic atmosphere as markedly as prolonged rotation.

It would seem from these findings that neither method measures "platelet stickiness" *per se* but rather a microcosm of the entire platelet-plasma coagulation system.

TABLE III
Distribution of Subjects by Age and Sex

Data	Normal		Arteriosclerotic	
	Men	Women	Men	Women
Decade				
20–30	9	3	1	0
30–40	11	1	3	0
40–50	14	0	11	0
50–60	8	0	14	1
60–70	5	0	6	2
70–80	2	0	14	0
	—	–	—	–
	49	4	49	3
Total no. subjects	53		52	
Mean age	42.4		57.7	
No. over 40 yr.	29		48	

TABLE IV
Adhesive Index

Subjects	Number	Determinations	Mean Adhesive Index
Normal	53	132	1.06 ± 0.08
Arteriosclerotic	52	123	1.11 ± 0.13
			$p > 0.02$

RESULTS

Adhesive Index in Normal Individuals and in Patients with Coronary Atherosclerosis: One hundred five subjects were studied. The breakdown by age, sex and diagnostic grouping is given in Table III. There were fifty-three normal volunteers and fifty-two patients. Almost all of the patients with coronary arteriosclerosis (forty-eight of fifty-two) were over 40 years of age, as compared with only twenty-nine of fifty-three in the control group.

The mean adhesive index in the normal group was 1.06 (Table IV). This did not appear to be influenced by age as the mean values for those over and under age 40 were the same. Of a total of 132 individual determinations on fifty-three subjects, there were fourteen determinations with an adhesive index of 1.19 or greater, involving three subjects. Two of these subjects were young men apparently in

TABLE V

Adhesive Index : Daily Variation

Name	Sex	Age	N*	Range	Mean	S.D.†	Diagnosis
Normal Subjects							
N. Mc.	F	36	18	1.06–1.17	1.11	±0.073	Normal
L. H.	M	38	8	0.99–1.16	1.10	±0.061	Normal
W. E.	M	29	6	1.01–1.10	1.08	±0.036	Normal
C. S.	M	46	5	0.96–1.05	1.00	±0.032	Normal
F. C.	M	29	9	1.20–1.34	1.28	±0.052	Normal
S. D.	F	24	9	0.88–1.11	0.97	±0.091	Normal
L. B.	F	24	10	0.96–1.10	1.04	±0.025	Normal
I. H.	M	48	5	1.01–1.07	1.04	±0.025	Normal
J. D.	M	37	7	0.98–1.07	1.03	±0.038	Normal
Arteriosclerotic Subjects							
R. E.	M	36	7	1.16–1.20	1.18	±0.017	ASHD
P. E.	M	54	5	0.90–1.00	0.93	±0.040	ASHD
J. S.	M	44	5	1.11–1.19	1.13	±0.028	ASHD
A. E.	M	71	7	1.00–1.21	1.12	±0.100	Diabetes, PVD
A. F.	M	65	8	1.01–1.11	1.05	±0.070	PVD, ASHD
J. P.	M	74	5	0.94–1.09	1.04	±0.060	ASHD
M. LeB.	M	22	5	1.01–1.23	1.10	±0.080	ASHD
R. G.	M	58	7	0.99–1.06	1.02	±0.085	ASHD
G. McD.	M	44	7	1.01–1.19	1.07	±0.060	ASHD, Hyp
A. M.	M	49	5	0.95–1.28	1.11	±0.120	ASHD
C. B.	M	48	6	1.00–1.10	1.06	±0.040	ASHD
A. L.	F	76	5	1.08–1.28	1.14	±0.080	CVD

NOTE: ASHD = arteriosclerotic heart disease; PVD = peripheral vascular disease; Hyp = hypertension; CVD = cerebrovascular disease.

* N = number of subjects.

† S.D. = standard deviation.

TABLE VI

Subjects with Arteriosclerosis

Breakdown	Normal	Mean Adhesive Index
All subjects with arteriosclerosis	52	1.11 ± 0.13
Myocardial infarction within 12 mo.	25	1.11
Myocardial infarction within 1 mo.	15	1.11
Angina pectoris	14	1.16
Old infarction (more than 1 yr.)	13	1.05
Recent infarction (within 12 mo.) and angina pectoris	39	1.14*

* The difference between the means of this group and the normal group is highly significant ($p > 0.001$).

good health, 28 and 29 years of age, and the third was a middle-aged male of 53 years in excellent health. The daily variability of the adhesive index in subjects with multiple determinations is shown in Table v.

In the group with coronary arteriosclerosis, the mean value for the adhesive index was 1.11 (Table IV). Of a total of 123 determinations on fifty-two subjects, there were twenty-two determinations with an adhesive index value of 1.19 or greater, involving sixteen subjects. Multiple determinations were done on ten of these subjects (a total of forty determinations yielding sixteen values of 1.19 or over). The daily variation of the adhesive index values is shown in Table v.

It would appear, therefore, that normal individuals show little day to day variation in their adhesive index and few high index values. Individuals with coronary arteriosclerosis as a

TABLE VII

Lipid Tolerance Test

Group	Subjects	Age	Fasting	2 Hours	4 Hours	6 Hours
			Red Blood Cells (in millions)			
Normal	25	40.8	5.24 ± 0.32	5.23 ± 0.35	5.23 ± 0.34	5.19 ± 0.37
Arteriosclerotic	25	53.2	4.76 ± 0.39	4.79 ± 0.37	4.75 ± 0.43	4.75 ± 0.43
			Platelets (in thousands)			
Normal	25	40.8	265.52 ± 73.9	261.29 ± 78.3	269.60 ± 76.0	266.84 ± 70.1
Arteriosclerotic	25	53.2	251.36 ± 61.9	254.12 ± 63.9	257.08 ± 69.2	244.48 ± 68.7
			Serum Triglycerides (mg. %)			
Normal	25	40.8	141.9 ± 64.0	225.9 ± 96.4	289.6 ± 154.8	210.1 ± 97.3
Arteriosclerotic	25	53.2	183.4 ± 69.8	249.8 ± 79.2	344.0 ± 119.4	318.4 ± 130.0
P			0.05	0.4	0.2	0.01
			Adhesive Index			
Normal	25	40.8	1.03 ± 0.06	1.04 ± 0.07	1.05 ± 0.06	1.04 ± 0.05
Arteriosclerotic	25	53.2	1.14 ± 0.12	1.19 ± 0.10	1.19 ± 0.09	1.14 ± 0.08
P			0.001	0.001	0.001	0.001
			Serum Cholesterol (mg. %)			
Normal	25	40.8	248.08 ± 54.8			
Arteriosclerotic	25	53.2	296.49 ± 60.2	...	...	...
P			0.01			

group have a higher mean adhesive index value and a greater intraindividual variability. When a more precise breakdown of the group with arteriosclerosis was attempted (Table VI), there appeared to be no significant differences in adhesive index between those subjects studied during the first month following infarction and those studied within the first year. The group with angina had adhesive indexes similar to those with myocardial infarction. However, the group of thirteen patients with remote infarction had adhesive index values comparable to the normals. When the data were recalculated excluding this group, the mean adhesive index for thirty-nine subjects with recent infarction and angina was 1.14. The difference between the means of the controls and of this selected group was highly significant statistically. This would suggest that the adhesive tendency may be a temporary phenomenon, not seen in the stabilized patient with arteriosclerotic heart disease but rather representing a more active process.

Effect of Acute Fat Loading on the Adhesive Index and Serum Lipids in Normal Individuals and Patients with Coronary Atherosclerosis: A fat breakfast, containing 75 gm. of mixed animal fats (butter, eggs, 40 per cent cream, bacon) was fed to twenty-five normal subjects and to an equal number of subjects with atherosclerosis. Blood was obtained in the fasting state, 2, 4 and 6 hours after the meal (Table VII). No significant differences were observed in the erythrocyte or platelet counts between or within the groups. The adhesive index was significantly higher in the abnormal group in the fasting state and showed a further increase following ingestion of fat, while the controls showed no change. None of the normals had an adhesive index greater than 1.19 in the fast-

TABLE VIII
Effect of Anticoagulants on the Adhesive Index

Response	No. of Cases	
Positive (rise in A.I.)		13
Treated with Danilone	9	
Treated with Sintrom	4	
Negative (no change or fall in A.I.)		11
Treated with Danilone	8	
Treated with Sintrom	3	
Suitable for analysis		24
Total number of cases		29

ing state, whereas six of the abnormal group exceeded this value. After the fat meal, an additional eleven subjects in the abnormal group exceeded 1.19 (the six subjects with high fasting adhesive indexes showed very little additional change following the high fat meal); of the eleven subjects whose adhesive indexes rose following the fat meal, nine showed a substantial rise (greater than 0.10) and two a slight rise only. At one time or another during the test seventeen of twenty-five (sixty-eight per cent) of the abnormal group exceeded 1.19, whereas none of the normals did so.

Significant differences between the two groups were also seen in the fasting levels of the serum triglycerides and cholesterol (Table VII). Following the high fat meal, triglycerides rose in both groups and the difference between the groups was obscured until the six-hour period when it again became significant. No correlation was noted between individual levels for triglycerides and the adhesive index. Whether or not a rise in adhesive index occurred following the high fat meal did not depend on serum triglycerides.

Serum cholesterol levels were significantly higher in the coronary group than in the controls. Fifty-six per cent of the coronary group had cholesterol levels of 300 mg. per cent or more as compared with 16 per cent in the control group. As with the serum triglycerides, there was no correlation between the adhesive index values and the cholesterol.

The data indicate a striking sensitivity of the adhesive index to the ingestion of fat in individuals with clinical coronary disease but not in normals. In nine of twenty-five, thirty-six per cent of the coronary group, a substantial rise in the adhesive index occurred following the fat meal. This could not be correlated

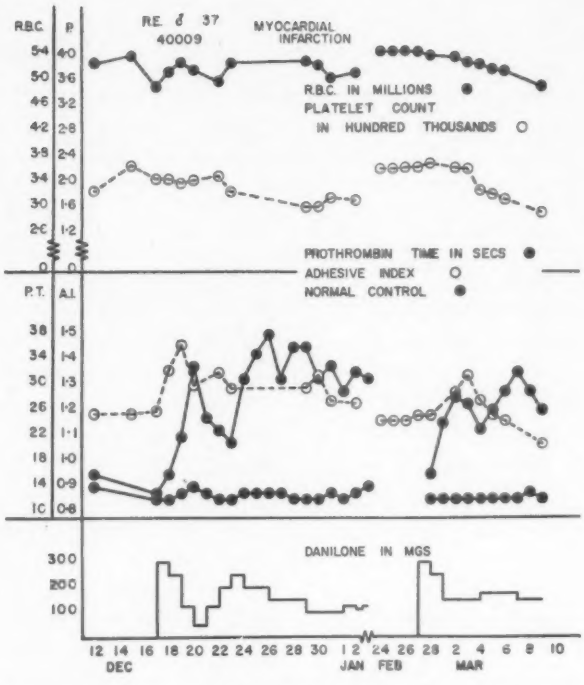


FIG. 1. Case 1. Previous administration of Danilone was followed by a sustained rise in adhesive index. In this and subsequent figures the graphs from above downward are: red blood cells in millions, platelet count in thousands, adhesive index in units, patient's prothrombin time and control prothrombin time in seconds.

with the measured levels of serum cholesterol or triglycerides or with changes in these factors after the test meal.

Effect of Anticoagulants on the Adhesive Index in Patients with Coronary Atherosclerosis and Coronary Insufficiency (Acute and Chronic): Twenty-nine subjects with coronary arteriosclerosis were were studied (Table VIII). The adhesive index was obtained at least once and preferably on several days before starting anticoagulants. It was followed daily thereafter until it stabilized or treatment was discontinued. Daily prothrombin times (one stage) were also included for these patients. Anticoagulants were prescribed by the house staff and attending physicians in the usually recommended doses. Five cases were excluded from the study. One patient received initial treatment with heparin, another received concurrently large doses of salicylates and a third had only recently discontinued anticoagulants. In a fourth patient a cerebral thrombosis occurred on the second day of treatment and was probably responsible for the marked rise in the adhesive index. The fifth patient was excluded because of inadequate data for the first two days of treatment.

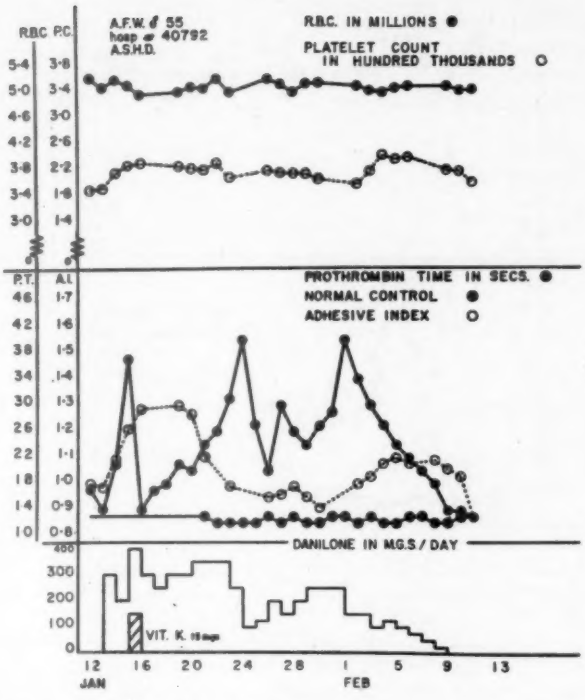


FIG. 2. Case 2. Two previous episodes of myocardial infarction. Danilone therapy resulted in an immediate rise in adhesive index. On the third day of treatment, he was inadvertently given twice the prescribed dose. Vitamin K_1 15 mg. was given intravenously as an antidote. Prothrombin time dropped rapidly to control levels, but adhesive index remained elevated for the next 5 days. Stepwise termination of Danilone treatment was associated with a transient rise in adhesive index.

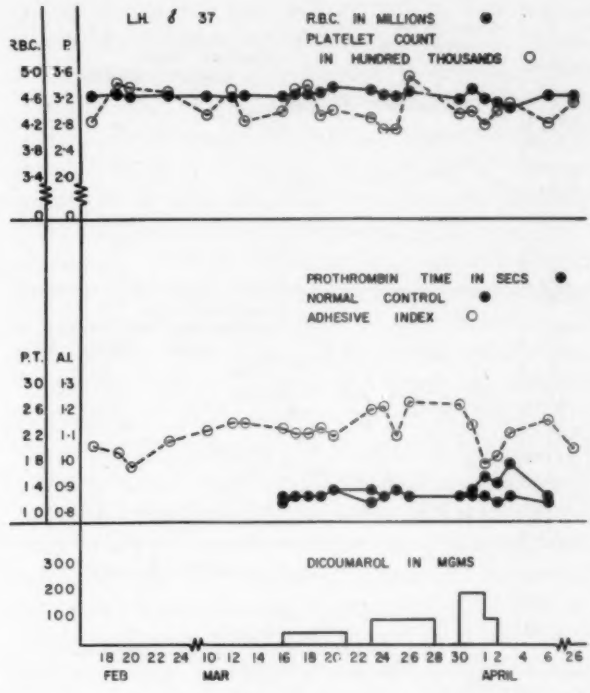


FIG. 3. Case 3. Healthy normal was given 50 mg. Dicumarol daily for 1 week and then 100 mg. daily for the second week with no significant change in prothombin time and a slight rise only in adhesive index. Increase in Dicumarol dosage to 200 mg. daily led to a rise in prothrombin time and a fall in the adhesive index.

A rise of 0.20 in the adhesive index, or a sustained rise of greater than 0.10 on several days, was taken as significant. Thirteen of twenty-four showed such a rise. In ten the adhesive index rose at least 0.20 unit and in three a sustained rise greater than 0.10 was noted (nine were receiving Danilone® and four, Sintrom®). Eleven of twenty-four showed no rise, and occasionally a fall, on anticoagulants (eight were receiving Danilone and three, Sintrom).

In general, the rise in adhesive index occurred during the first 72 hours of anticoagulant therapy when prothrombin times were not yet in the therapeutic range (less than 25 seconds). With the rise in prothrombin time to therapeutic levels, the adhesive index fell in almost all cases.

The pattern of response can best be illustrated with specimen cases:

CASE 1. R. E., a male, age 37 (Fig. 1), with a 3 year history of angina, and acute myocardial infarction 1 year prior to admission. He was admitted for institution of long term anticoagulant treatment. Administration of the usual dosage of Danilone was followed by an immediate rise in adhesive index, and despite the attainment of adequate prothrombin times the adhesive index never quite returned to base line. After discharge the patient discontinued Danilone. He had three severe anginal attacks and returned to the hospital. Treatment with Danilone was again followed by a rise in adhesive index.

CASE 2. A. F. W., a male, age 55 (Fig. 2), had sustained two episodes of myocardial infarction, the first in 1951 and the second in 1958, 1 year prior to admission. The last episode was followed by angina and persistent auricular flutter. Anticoagulant therapy with Danilone was undertaken as a prelude to attempting conversion of the flutter to sinus rhythm. An immediate rise in adhesive index followed the institution of Danilone therapy. On the third day of treatment he was inadvertently given 400 mg. of Danilone (double the prescribed dose). The physician on duty became alarmed and gave him 15 mg. vitamin K_1 intravenously. His prothrombin time dropped rapidly to control levels, but his adhesive index remained elevated for the next 5 days. After several days of treatment with large doses of Danilone, his prothrombin time

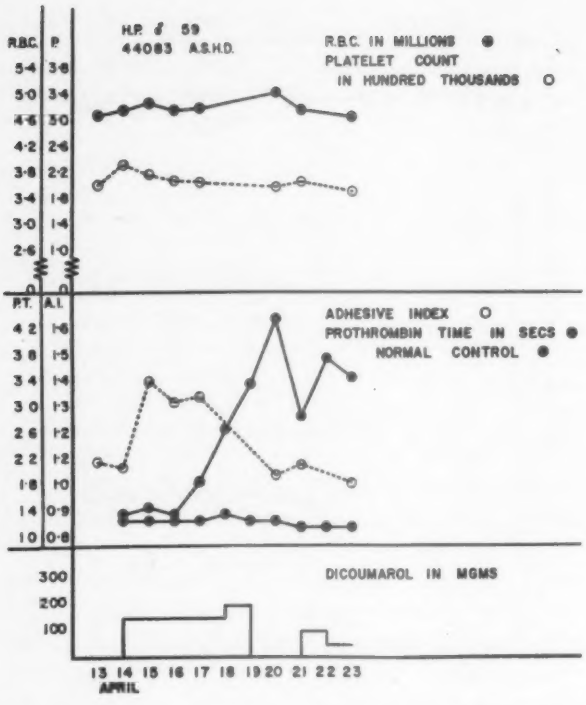


FIG. 4. Case 4. Previous myocardial infarction and angina of effort. Treatment with 100 mg. Dicumarol daily resulted in a sharp initial rise in adhesive index with only minimal changes in the prothrombin time.

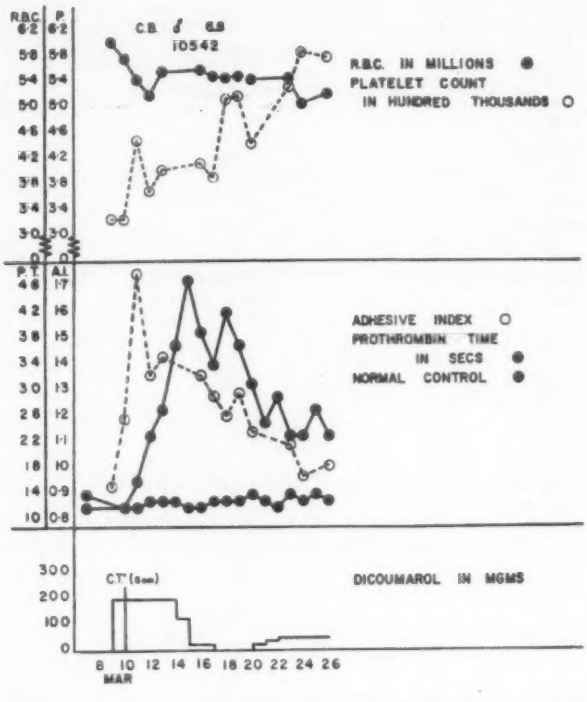


FIG. 5. Case 5. Acute myocardial infarction. Initial adhesive index was low. On March 9 at 11:00 P.M., patient received 200 mg. Dicumarol. At 6:00 A.M. the next morning, he was found to have suffered a cerebral thrombosis. The adhesive index rose to very high values during this episode and then fell steadily as prothrombin times rose. The initial platelet count was low and showed a steady rise.

again rose and coincidentally the adhesive index fell to normal levels. Stepwise termination of Danilone treatment was associated with a transient rise in adhesive index.

Because thirteen of twenty-four (54 per cent) of our subjects showed an initial rise in adhesive index following institution of anticoagulant therapy, it was suspected that this might be due to inadequate dosage or delay in achieving adequate therapeutic prothrombin time levels or both. Accordingly, eleven subjects (two normals and nine with coronary disease) were deliberately treated with small doses of Dicumarol® (100 mg. per day) for several days.

CASE 3. L. H., a male, age 37 (Fig. 3), was a healthy control. He took Dicumarol 50 mg. daily, for 6 days with no change in either his prothrombin time or adhesive index. The dose was then increased to 100 mg. daily. There was no change in prothrombin time but a slight rise in adhesive index. A further increase in dosage to 200 mg. daily resulted in a slight rise in prothrombin time and a fall in adhesive index.

CASE 4. H. P., a male, age 59 (Fig. 4), had a myocardial infarction 3 years prior to admission and angina of effort since. Treatment with 100 mg. Dicumarol daily resulted in a sharp initial rise in adhesive index with only minimal changes in the prothrombin time.

Five of nine subjects with ischemic heart disease showed a rise in adhesive index upon treatment with small doses of Dicumarol. Since only two normal subjects were studied, we cannot say whether the rise in adhesive index following small doses of Dicumarol is specific only for patients with ischemic heart disease. Nor can we say that it is specifically a dose-related response since only a little over 50 per cent of subjects tested at both low and high dosage levels gave a positive response. It is probably a qualitative response indicating a temporary hypercoagulable phase which may occur in an unknown number (presumably more than half) of patients undergoing treatment with anticoagulants.

Adhesive Index and Thrombotic Processes: Moolten and Vroman[22] in their original work on the adhesive index claimed that it was a sensitive indicator of thrombotic processes in the body. This was confirmed by Bobek and Cepelak's[23] study of acute thrombophlebitis. From ob-

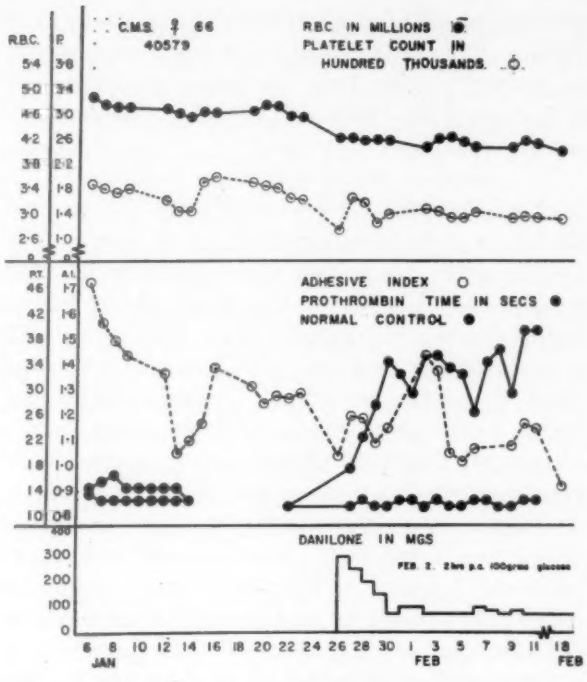


FIG. 6. Case 6. Recent cerebral thrombosis. Adhesive index was very high and fell spontaneously without treatment. Subsequent treatment with Danilone resulted in a transient rise in adhesive index.

servations on several cases we can add confirmatory data.

CASE 5. C. B., a male, age 68 (Fig. 5), had sustained a mild myocardial infarction 3 days prior to admission. His initial adhesive index was low. On March 9 at 11:00 P.M. he received 200 mg. of Dicumarol. At 6:00 A.M. the next morning he was found to have suffered a cerebral thrombosis. His adhesive index rose to very high values during this episode, and on the next day fell steadily as the prothrombin time values rose. The platelet count was low at the beginning and showed a steady rise. This probably represents the initial removal of large numbers of sticky platelets and then subsequent replacement by more normal platelets.

CASE 6. C. S., a female, age 66 (Fig. 6), was admitted with a history very suggestive of recent cerebral thrombosis. Her initial adhesive index was very high (greater than 1.70) and fell spontaneously without treatment. She was subsequently given Danilone and showed a transient rise in adhesive index.

COMMENTS

The results recorded here suggest that persons with ischemic heart disease have a higher adhesive index than do normals and also a greater day to day variability of their index values. They are also more sensitive to the effects of a high fat meal in that the adhesive index tends to rise following it, whereas it remains unaltered in normals.

Increased Clotting Mechanisms in Ischemic Heart Disease: Since the adhesive index appears to be intimately related to changes in platelet environment,[21] a rise in adhesive index may be taken to mean an increased tendency toward clotting. (See Materials and Methods.) An increased tendency toward clotting in ischemic heart disease has been proposed by several workers. As early as 1946, Meyers and Poindexter[24] demonstrated a shortening of the dilute prothrombin time in patients with myocardial infarction. This was confirmed by others.[25,26] Also in 1946, Ogura[2] demonstrated accelerated clotting after myocardial infarction, using the heparin-retarded clotting time. It is of interest that he found accelerated clotting most marked between the second and seventeenth days after onset of infarction and concluded that accelerated coagulation followed the attack rather than preceded it. Using the heparin-retarded clotting time technic, Rosenthal and Weaver[3] demonstrated accelerated coagulability in 74 per cent of patients with acute myocardial infarction but not in patients with chronic arteriosclerotic heart disease.

Gormsen[7] carefully standardized the heparin-retarded clotting time test and reported shortened clotting times in patients with angina pectoris and also following acute myocardial infarction. Holger-Madsen[8] extended and verified these observations using Gormsen's technic, as well as a very sensitive heparin-thrombin test of his own design. In 1957 Poller[27] reported that in a group of patients suffering from recent thromboembolic disorders there was a significant increase in plasma factor VII activity. He postulated that the increased factor VII activity might be a causative factor in the production of thrombosis, neutralizing the natural anticoagulant heparin and upsetting the balance of coagulation.[28] This role is suggested by the experimental work of Wessler,[29] who produced rapid thrombosis in animals by infusion of serum rich in factor VII activity.

An alternative explanation might be that the increased factor VII activity (or decreased heparin resistance and all the indexes it affects) is the result of a release of tissue factors from ischemic tissue or of serum factors from the thrombus. It is well known that several enzymes are released into the circulation by injured tissue.[30] Serum glutamic oxalacetic transaminase

(SGOT), serum aldolase and serum oxidase are a few of the enzymes released by infarcted myocardium within 1/2 hour to 1 hour of damage. The possibility that other thromboplastic materials might be released cannot be overlooked. This correlates with the observations[22,31,32] of increased platelet stickiness following trauma, surgery or childbirth and the increased incidence of thromboembolism at these times.

The possibility that active ischemic heart disease may result in the intermittent release of thrombogenic material may explain the intermittent variations in the adhesive index observed by McDonald and Edgill[10] and by ourselves. It may also serve to explain the increased sensitivity of the clotting mechanism to fat meals on the basis of a diminished reserve of the natural anticoagulant, heparin. It is more consistent with the fact that coronary thrombosis is a relatively late event in myocardial ischemia or infarction. Thus, Spain and Bradess[33] found coronary thrombi in only sixteen per cent of 303 cases of myocardial infarction surviving less than 1 hour, in 37 per cent of sixty-five cases surviving 1 to 24 hours and in 54 per cent of 200 cases surviving 24 hours. They stated that "coronary thrombi may perhaps play only a secondary role in the precipitation of acute myocardial ischemic episodes."

Transient Increased Coagulability Following Administration of Anticoagulants: What of the increased adhesive index or coagulability observed temporarily in 50 per cent of our patients treated with Danilone or Sintrom and Dicumarol? A study of the literature has yielded little supportive evidence for this finding, perhaps because few observations have been made during the first 24 to 72 hours of anticoagulant treatment.

Spooner and Meyer[34] and Wright[35] have reported that platelet adhesiveness falls following Dicumarol therapy. The first two workers[34] studied thirty-three patients and made their first observations on the fourth day of treatment and again on the seventh and tenth days. They observed no change in adhesiveness on the fourth day despite a minor prolongation of the prothrombin time (14 seconds, control 11.5 seconds). There was a fall in adhesiveness on the seventh day when the prothrombin time was 20.5 seconds. Wright[35] studied rabbits and made her first observations on the seventh day of treatment. She concluded that changes in platelet stickiness ran parallel to the prothrombin time. Failure to study the changes occurring in the first 72 hours of treatment might explain the difference between our results and those just cited.

In thirty-two unselected ward patients, Lewitus[36] studied the effects of 100 mg. Dicumarol daily on the prothrombin time (one stage Quick) and coagulation time (modified method of Halse). In 98 per cent of the patients the shortest coagulation time was seen with a prothrombin activity of 50 per cent, the time often being shorter in this range than in the 100 per cent prothrombin activity range. It is of interest that four of thirty-two patients with prothrombin levels of about 50 per cent and a shortened coagulation time developed thrombophlebitis. Poller,[6] in a study of forty-three patients treated with Dicumarol, observed accelerated clotting in eleven instances when the prothrombin time was less than 30 per cent.

Gormsen[7] reported that in patients treated with Danilone the heparin-retarded clotting time was often lengthened after 3 to 5 days to between 15 and 25 minutes (normal 10 to 15 minutes), but in most debilitated patients clotting time was not prolonged until treatment had been given for 1 to 3 weeks. This persistently shortened heparin-retarded clotting time was observed despite prothrombin times (P-P times of Owren) in the therapeutic range. Similarly, Holger-Madsen[8] noted maximum shortening of the heparin-thrombin time on the fourth to tenth day after the onset of myocardial infarction despite prothrombin times within the therapeutic range.

Two possible explanations are: (1) The rise in adhesive index (or the shortened clotting time) represents changes due to release of thromboplastic materials following infarction. This could explain the changes following acute infarction, but it was probably not true in our series in which a rise in adhesive index was seen in subjects with chronic coronary insufficiency (not acute infarction) given anticoagulants on an elective (prophylactic) basis. They generally had low indexes prior to treatment. (2) The rise in adhesive index is a temporary result of a disturbance in the body's clotting system produced by the anticoagulant.

At the present time we have no explanation for this phenomenon. It does not appear to be dose-related, but rather some sort of qualitative effect. Because of its transient nature in most subjects, it is probably not of much

clinical significance. Whether it persists with very low dosage levels of anticoagulants over long periods of time is another intriguing question to which no answer can be given at present.

Summary and Conclusions

1. The adhesive index, as described by Moolten and Vroman, was determined in fifty-three normal subjects and fifty-two patients with clinical manifestations of arteriosclerosis of the coronary or peripheral vessels or both.

2. The mean value for the adhesive index in the normal group was 1.06 ± 0.08, and for the arteriosclerotic group 1.11 ± 0.13. In the latter group no significant differences in adhesive index were found between those who had sustained a myocardial infarction within the past 12 months and those with angina pectoris. Subjects with old infarction (more than 1 year) had an adhesive index value of 1.05. In the thirty-nine patients with angina pectoris and recent myocardial infarction, the adhesive index was 1.14. This value was significantly higher than that for the control ($p > 0.001$).

3. Serial determinations of the adhesive index in the control group revealed a relatively narrow range of values for any individual subject. Patients with coronary disease showed a more marked day to day variation.

4. A high fat breakfast (75 gm. animal fat) was administered to twenty-five healthy subjects and twenty-five patients with coronary disease who were not receiving anticoagulants. None of the control subjects showed a significant rise in adhesive index despite substantial increases in the serum triglyceride levels. Six patients had initially high values for the adhesive index, and a further eleven had a significant rise following the test meal. Whether or not the adhesive index rose did not appear to be related to triglyceride or cholesterol levels.

5. Twenty-nine subjects with coronary disease were treated with oral anticoagulants in the usually recommended dosage. Twenty-four cases were suitable for analysis. Thirteen patients showed a rise in adhesive index during the first 72 hours of anticoagulant treatment. Nine more subjects with coronary disease were deliberately treated with a relatively small dose of Dicumarol (100 mg. daily). Five of these showed a significant rise in the adhesive index in the first 72 hours of treatment.

6. The adhesive index is a sensitive indicator of thrombosis *in vivo*.

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Determination of Prothrombin Concentration as an Index of Anticoagulant Control*

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IN SPITE OF the intensive efforts of many hematologists, the precise sequence of events producing coagulation of blood remains obscure. The application of results of *in vitro* studies to an understanding of coagulation *in vivo* has proved a troublesome and perilous transition to the clinician in his attempt to devise effective means for the prevention of intravascular thrombosis and embolism without at the same time invoking the hazard of hemorrhage. The increasing use of coumarin-type anticoagulants for long periods in both hospitalized and ambulatory patients has brought into focus the deficiencies in the present methods used to determine appropriate therapeutic administration of these drugs. The one-stage prothrombin test of Quick has been the method of choice for years, in spite of the realization of its shortcomings.[1-11] Several authors have reported the value of determining prothrombin concentration during anticoagulant therapy.[1,3,4,5,6,9,12] It is the purpose of this paper to present further observations on the value of prothrombin concentration determinations during anticoagulant therapy with warfarin (Coumadin®) sodium.

METHODS

Two groups of fifty and 280 patients, respectively, were studied. During an 18 month period, 2,500 blood samples were collected for the simultaneous determination of the one-stage prothrombin time by the method of Quick[13,14] and the prothrombin concentration by the Biggs modification of the Owren-Aas method.[6,15,16] Simultaneous determination of proconvertin (factor VII) concentration by the method of Owren and Aas[6] was performed in twelve of the patients in group 1 and in five of the patients in group 2. The laboratory determinations were performed the same morning that the blood samples were drawn. All of the laboratory determinations of the concentration of prothrombin and proconvertin were performed by the same technician. "Quality control" was utilized in the prothrombin determination.[16]

Group 1: Fifty patients who had not previously received anticoagulants and who had no overt evidence of a coagulation defect were given warfarin sodium and daily prothrombin time and prothrombin concentration determinations were obtained. Five of the patients received the initial dose of warfarin sodium intravenously and all subsequent doses orally. The remaining forty-five patients received all doses of the drug orally. The initial dosage varied from 37.5 to 100 mg., depending on the size and the age of the patient. Appropriate adjustments in dosages were made in relation to the prothrombin concentration as well as to the prothrombin time. In those patients in whom the Quick time did not fall below 6 to 8 per cent activity, the prothrombin concentration was used exclusively as a dosage guide. In ten of the patients, the Quick time was completely ignored until the prothrombin concentration had fallen within therapeutic levels; namely, 10 to 24 per cent of normal.[1,12] The dosage of warfarin sodium was given each afternoon following receipt of the report on the blood sample drawn on the morning of the same day. Twenty-two patients received heparin in addition to the more slowly acting anticoagulant, warfarin sodium, until the prothrombin concentration had reached therapeutic levels.

Group 1 included thirty-two patients with a diagnosis of myocardial infarction, eight patients with thrombophlebitis, four patients with pulmonary emboli, four patients with cerebral thrombosis and two patients with rheumatic heart disease, atrial fibrillation and peripheral arterial emboli.

Group 2: Two hundred and eighty patients on long-term anticoagulant therapy were observed on an out-patient basis at intervals varying from 1 week to 1 month over a period of 18 months. A pro-

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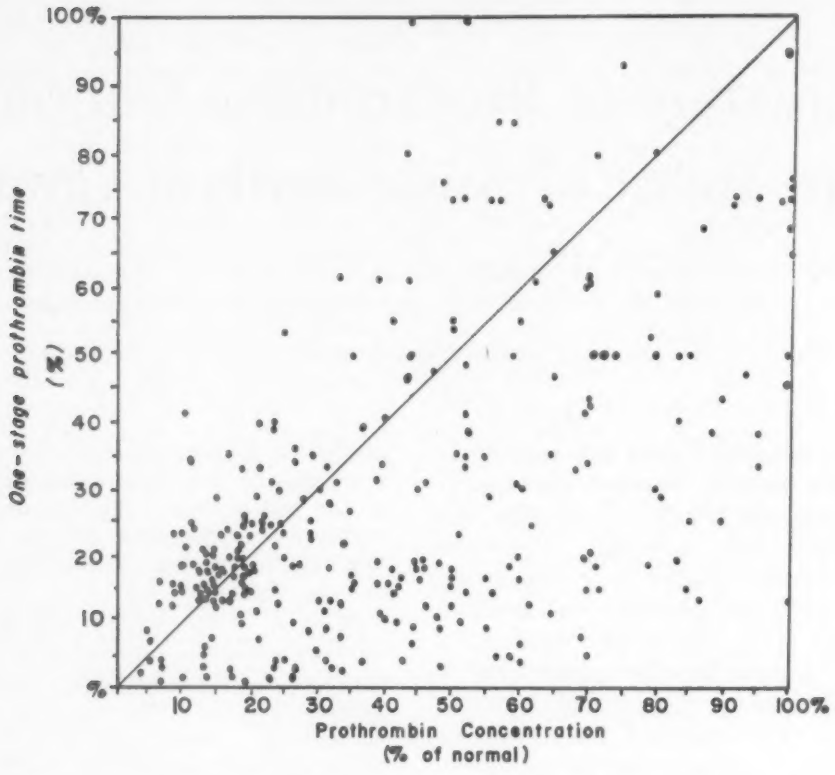


FIG. 1. Analysis of the prothrombin concentration and the one-stage prothrombin time in 300 blood samples.

thrombin time and a prothrombin concentration were determined at the time of each visit. The patients in this group were chosen from the Out-Patient Clinic of Hermann Hospital and from the private practice of three of us.

RESULTS

Correlation of Simultaneous Prothrombin Times and Prothrombin Concentrations: Figure 1 is an analysis of 300 representative samples obtained from both groups of patients. This analysis affords evidence of the lack of identity between results of one-stage prothrombin time and determinations of prothrombin concentration. The more nearly linear relationship of the prothrombin time to the proconvertin (factor VII) concentration as measured in 100 blood samples can be seen in Figure 2. The values for the prothrombin time and the prothrombin concentration in the patients in group 1 during the first 10 days of therapy are shown in Figures 3A and 3B, respectively. The average daily values of these two determinations are illustrated in Figure 3C. The prothrombin time can be noted to reach desired levels in the majority of the cases within the first 48 hours following the initiation of anticoagulant therapy. The prothrombin concentration, however, was reduced more gradually, and at the end of the first 48 hour period only one of the fifty patients studied could be considered to be within the desired range of prothrombin concentration (10 to 24 per cent). In Figure 4 is a bar graph depicting the daily accessions to the therapeutically effective range derived from fifty patients who received anticoagulant treatment with warfarin on the first day. The prothrombin had been reduced to less than 24 per cent of normal values in approximately half of the patients by the fifth day and in all of the patients by the tenth day. No significant difference was noted in the rate of reduction of prothrombin concentration in patients who received the initial dose of warfarin sodium intravenously or in twenty-two patients who received heparin plus warfarin orally during the first few days when compared with the group receiving only orally administered warfarin.

The range of the prothrombin concentration in 280 patients (on long-term anticoagulant therapy) whose prothrombin time was between two and two and one-half times the control value is shown in Fig. 5. The prothrombin

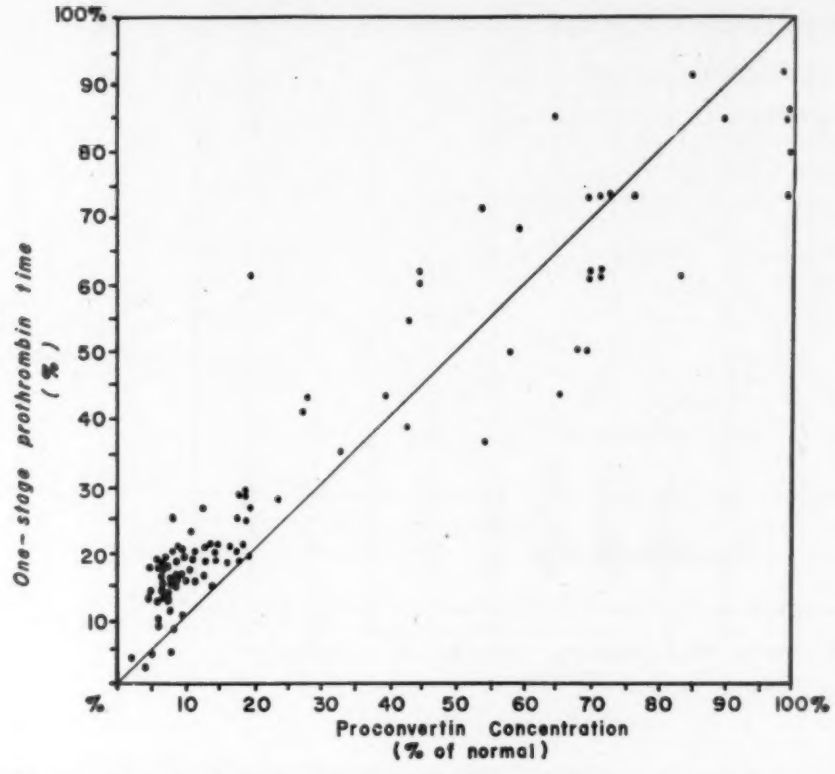


FIG. 2. Analysis of the proconvertin concentration (factor VII) and the one-stage prothrombin time in 100 blood samples.

concentration was greater than 24 per cent of normal in 9 per cent of the patients and less than 10 per cent of normal in 21.5 per cent of the patients. Thus, 30 per cent of these patients would be considered "out-of-control" by the prothrombin concentration determination. The range of the prothrombin time in the same group of patients whose prothrombin concentration was between 10 per cent and 24 per cent of normal is shown in Figure 6. The Quick time was less than twice the control value in 63 per cent of the cases and greater than two and a half times the control in 4 per cent of the cases.

There was no constant numerical relationship between the prothrombin time and the prothrombin concentration in either of the groups studied or even in the same subject on different clinic visits. The Quick time varied from 18 per cent to 50 per cent during a period when the prothrombin concentration remained constant. The prothrombin concentration varied from 6 per cent to 21 per cent of normal during a period when the prothrombin time remained constant.

Relation between Hemorrhage and Prothrombin Concentration: The prothrombin concentration was deliberately allowed to fall below 10 per cent in a number of the patients under close observation in the hospital in an attempt to determine whether there might be any relationship between the level of prothrombin and the occurrence of hemorrhage. In the absence of a demonstrable lesion as a source of bleeding, hemorrhage occurred most frequently from the urinary tract. Although there was no constant relationship between the occurrence of hemorrhage and the numerical value of the prothrombin concentration, this concentration was less than 10 per cent in all of the cases in which hemorrhage occurred. There were several exceptions, namely those cases which had a demonstrable pathologic lesion as the site of bleeding and two instances in which the bleeding was due to excessive doses of heparin sodium. One patient had four teeth extracted at a time when the prothrombin concentration was only 5 per cent of normal and the prothrombin time was 35 seconds (control 13 seconds). The prothrombin time the following day was prolonged to 43 seconds and the prothrombin concentration was 9 per cent of normal, there was, however, no apparent abnormal bleeding.

In this series an asymptomatic adenocar-

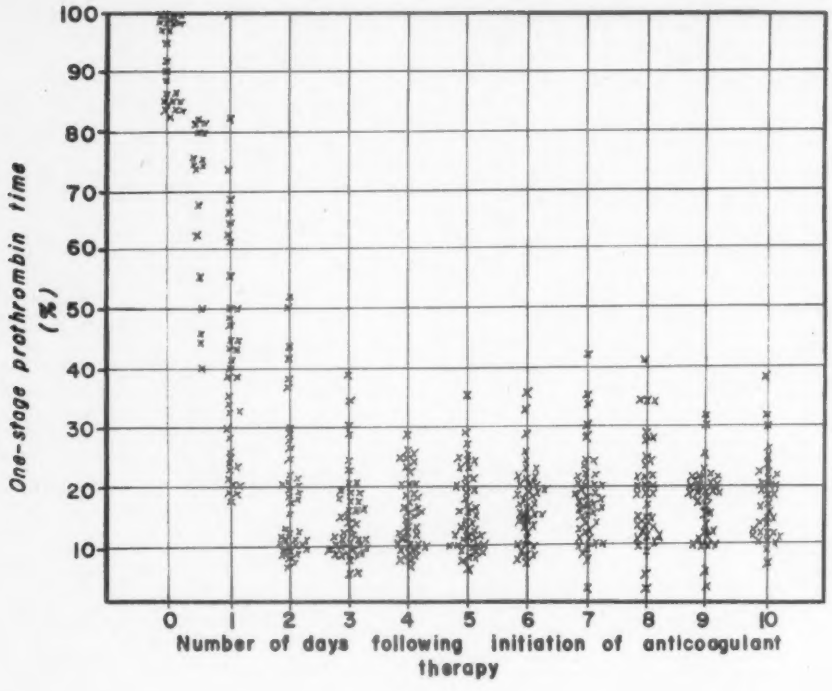


FIG. 3A. One-stage prothrombin time in fifty patients receiving warfarin sodium.

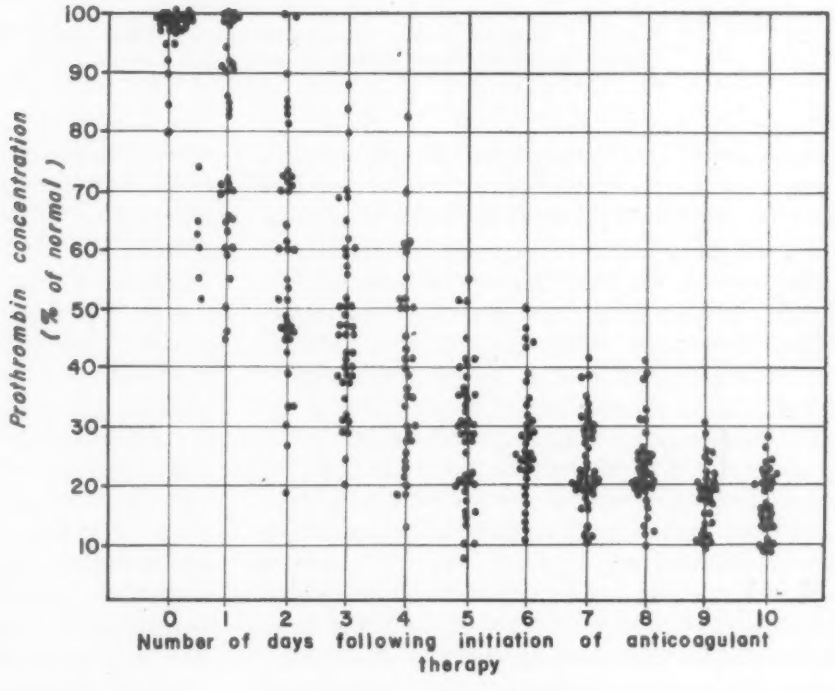


FIG. 3B. Prothrombin concentration in fifty patients receiving warfarin sodium.

cinoma of the rectosigmoid was responsible for gastrointestinal hemorrhage in one patient whose prothrombin concentration was approximately 20 per cent, with a prothrombin time of 25 seconds (control 13 seconds). In this admittedly selective series, wherein only those cases with simultaneous determinations of prothrombin time and prothrombin concentration were included, definite evidence of thromboembolism was observed in only one case. This patient experienced pulmonary embolism while receiving anticoagulant therapy instituted after an acute myocardial infarction. The prothrombin time immediately after oc-

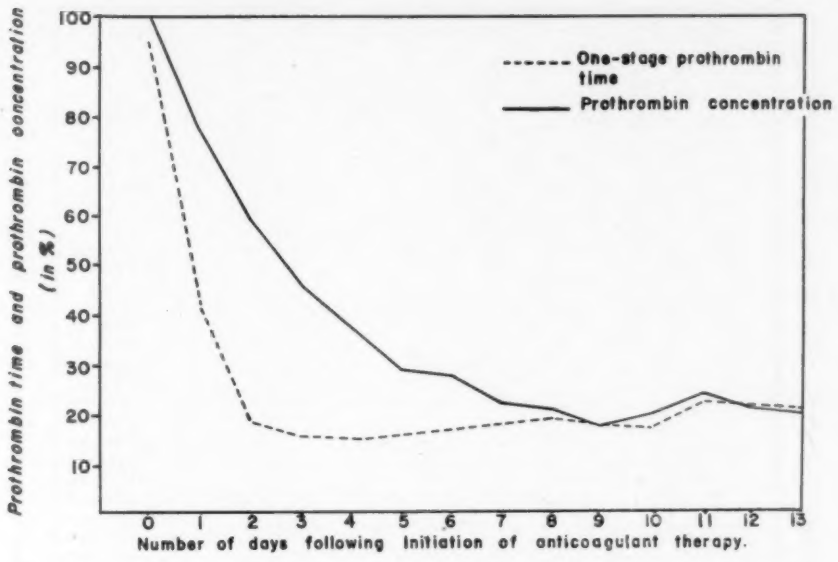


FIG. 3C. Averages of the prothrombin concentration and the one-stage prothrombin time in fifty patients receiving warfarin sodium.

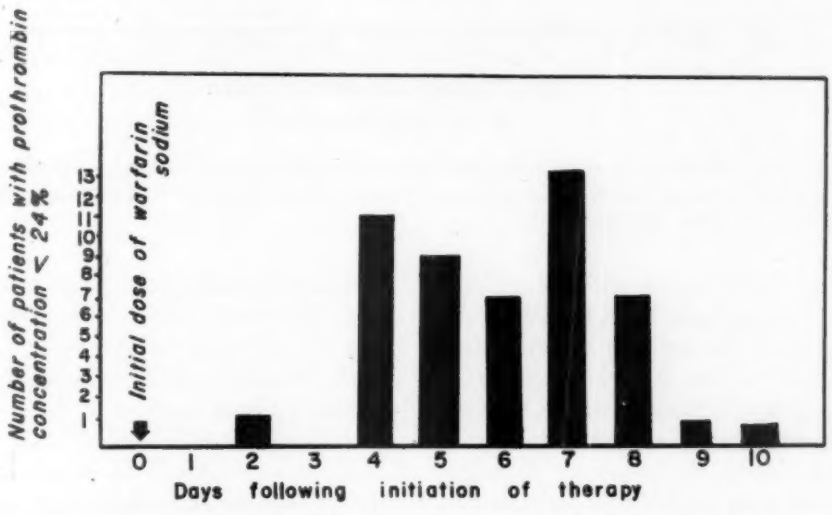


FIG. 4. Time required for fifty patients to reach therapeutic levels of hypoprothrombinemia (prothrombin concentration = 10 to 24 per cent) after beginning anticoagulant therapy.

currence of embolism was 30 seconds (14 per cent) and the prothrombin concentration was 46 per cent.

We had opportunity to study the findings at necropsy on one patient with pulmonary hypertension secondary to multiple small pulmonary emboli. At the time of death, the prothrombin time had been prolonged to 197 seconds (control 13 seconds) and the prothrombin concentration was 11 per cent. There was no evidence of hemorrhage.

The observation was made that the daily maintenance dosage for warfarin sodium paralleled the rapidity of reduction of prothrombin concentration during initiation of anticoagulant therapy; i.e., those patients who exhibited a fairly rapid fall in the prothrombin concentration in general required smaller daily maintenance doses of warfarin sodium.

COMMENTS

There are numerous references in the literature to the "hypoprothrombinemia" which occurs within the first two days following the

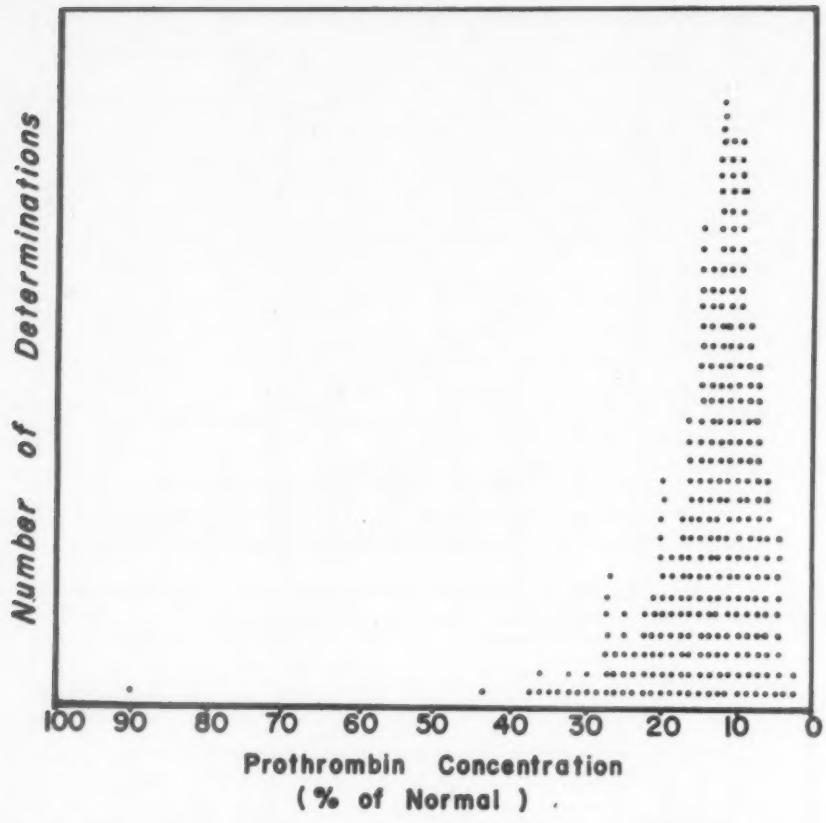


FIG. 5. Range of prothrombin concentration in 280 patients within therapeutic control levels as measured by the one-stage prothrombin time (two to two and one-half times the control value).

initiation of anticoagulant therapy.[17–22] These observations have apparently been based on the false assumption that the early prolongation of the one-stage prothrombin time represented a reduction in the plasma concentration of prothrombin. The one-stage prothrombin time of Quick has been shown to measure multiple clotting factors and may reflect a reduction in a single factor or in a combination of two or more of the factors which influence this test; namely, prothrombin,[23] factor VII,[23,24] factor V[25–27] and Stuart-Prower factor.[11–29] Although some of the other factors may influence the results of this test, the significance of their role is not clear at this time.

The coumarin-type anticoagulants have been shown to cause a reduction in several of the clotting factors, including prothrombin, factor VII, factor X and Christmas factor.[11,23,24,30,31,32] The most marked effect is seen initially in the reduction in factor VII. This apparently accounts for the early prolongation of the Quick time during anticoagulant therapy with the coumarin drugs. Plasma prothrombin level falls more slowly over a period of several days and is seemingly unrelated to the rate of reduction of factor VII. The discrepancy in the rate of reduction of these two factors may be explained by a relatively rapid turnover rate of factor VII as compared to the other clotting factors involved. Frick[33] has calculated the half-life of factor VII to be from 7.2 to 10.8 hours. Although data are not available at this time on the turnover of prothrombin, a longer half-life is suggested by the relatively slower reduction of prothrombin levels following initiation of anticoagulant therapy. A longer half-life of prothrombin would also explain those fairly wide daily fluctuations in the Quick time which were noted to occur without an accompanying change in the prothrombin concentration in patients receiving anticoagulants. Thus, the so-called "hypoprothrombinemia" of the first few days of anticoagulant therapy is in actuality hypoproconvertinemia and may occur initially in association with a normal plasma concentration of prothrombin. The true clinical significance of this observation is subject for speculation, but it may afford an explanation of the lack of

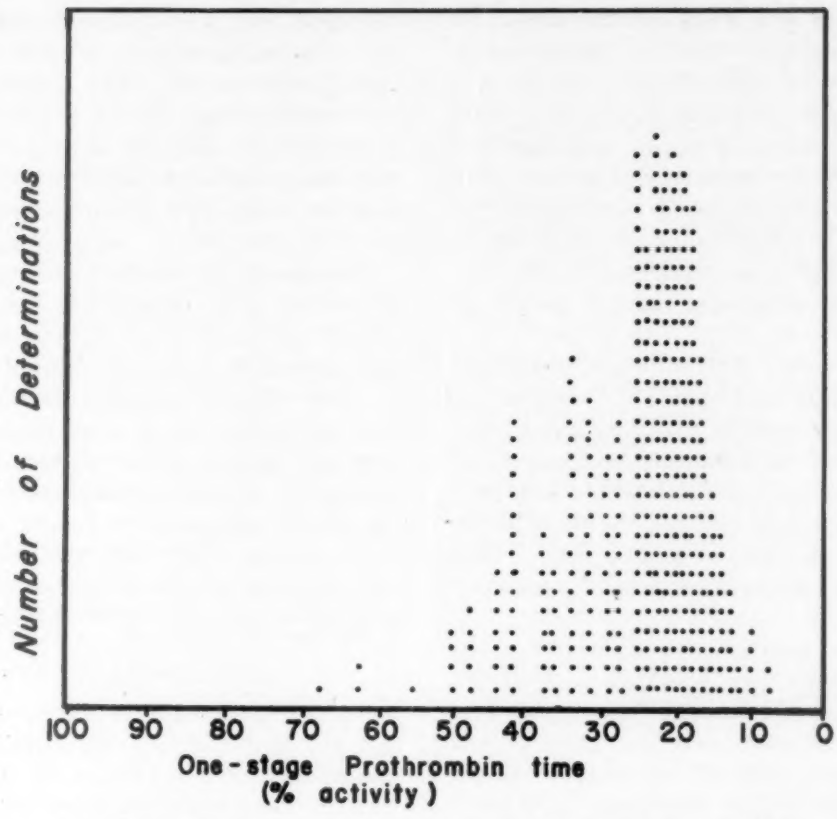


FIG. 6. Range of one-stage prothrombin time in 280 patients within therapeutic control levels as measured by the prothrombin concentration (10 to 24 per cent of normal).

correlation between the one-stage prothrombin time and the episodes of hemorrhage and thromboembolism.

Factor VII: A brief review of current information concerning the function of factor VII would seem essential to critical analysis of the data presented here.

1. It would seem from the data generally available that the function of factor VII is principally confined to the conversion of prothrombin to thrombin in the presence of tissue thromboplastin. However, the blood from patients deficient in factor VII will clot normally in the absence of tissue thromboplastin.[24] This suggests that factor VII may be concerned mainly with hemostasis and may not be essential to the intrinsic blood clotting system.[1,24,29,34,35]

2. Owren has shown that only a part of the proconvertin present in plasma is activated during the normal clotting process with a residual proconvertin activity from 70 to 90 per cent of normal.[23] Although the quantity of proconvertin present influences the amount of convertin formed, apparently only a relatively small quantity of convertin is necessary to "catalyze" the conversion of prothrombin initially. The conversion of prothrombin to thrombin, on the other hand, is a stoichiometric reaction and appears to be more intimately related to concentration of prothrombin than to the amount of proconvertin or convertin present.

3. Ackroyd[24] in reviewing the function of factor VII concluded that it is not essential in the coagulation of human blood when this occurs without the addition of tissue extracts.

4. Analysis of the reported cases of deficiency of factor VII reveals that bleeding occurs most often into the skin, from the alimentary tract or nose and into the joints. Hemorrhage in patients receiving coumarin-type anticoagulants is usually from the genitourinary tract.

5. In the majority of cases of symptomatic factor VII deficiency, the one-stage prothrombin time is considerably more prolonged than is ordinarily encountered in patients receiving coumarin drugs, even at the time of hemorrhage.

Clinical Applications of Data: These observations, together with the data reported herein, indicate, therefore, that the one-stage prothrom-

bin time of Quick is a more sensitive indicator of factor VII activity than of prothrombin. This is in agreement with previous reports.[1,3,16] In the light of this information it would seem that the most logical goal in anticoagulant therapy should be the reduction of prothrombin rather than the reduction of factor VII. If this is the case, it would be more important to the clinician to know the plasma concentration of prothrombin than the concentration of factor VII.

In view of the delay in reduction of prothrombin after beginning anticoagulant therapy, it is logical that rapid-acting anticoagulants such as heparin should be continued until a therapeutic level of hypoprothrombinemia has been achieved. This would prolong the usual duration of heparin therapy to a time 5 to 7 days after beginning therapy with the coumarin drugs.

In the group of patients on long term therapy whose prothrombin time was from two to two and a half times the control value, the prothrombin concentration was less than 10 per cent of normal values in 21.5 per cent. In the group of patients whose prothrombin concentration ranged from 10 to 24 per cent of normal, the Quick time was less than twice the control value in 63 per cent of the cases. These findings suggest that the usually accepted therapeutic range of prothrombin time (two to two and a half times the control value) is excessive in a large percentage of the cases. Many of these cases on long term treatment could have been given smaller doses of anticoagulant with adequate therapeutic control and with a decrease in the risk of hemorrhagic complications. Thus, the usually accepted limits for the prothrombin time must be subjected to reconsideration in the patients on long term anticoagulant therapy.

A consistently positive correlation between the level of prothrombin and the occurrence of hemorrhage or thromboembolism was observed in this study. Although numerous prothrombin values of less than 10 per cent of normal were observed, the majority were recorded in patients who exhibited no evidence of hemorrhage; however, no instance of hemorrhage was observed among patients whose prothrombin concentration was greater than 10 per cent of normal, except in the presence of a demonstrable lesion at the site of bleeding, and in two instances where bleeding was ascribed to excessive doses of heparin. It would seem, therefore, that 10 per cent of normal prothrombin concentration is a safe lower limit for the therapeutic range. The upper level of the therapeutic range was 24 per cent as previously suggested by Sise et al.[1,12] No evidence of thromboembolic phenomena was recognized in patients who had prothrombin levels lower than 24 per cent.

The prothrombin concentration test as performed in cases included in this study is technically more difficult and time-consuming than the one-stage prothrombin time of Quick. In view of the frequently similar values of the two tests following the tenth day of therapy with warfarin sodium, it seems logical that periodic sampling of the prothrombin concentration should be adequate for proper care of patients who are on long term anticoagulant therapy and on whom periodic tests of prothrombin activity by the method of Quick are done.

Conclusions and Summary

1. In patients receiving warfarin sodium, the prothrombin concentration does not fall to therapeutic levels (10 to 24 per cent) until 5 to 7 days after initiation of therapy. The range of variation noted was from 2 to 10 days. The initial prolongation of the one-stage prothrombin time is apparently the result of a relatively early fall in the concentration of factor VII (proconvertin), as compared with other clotting factors which influence results of the test.

2. In view of the fact that the action of factor VII is apparently primarily hemostatic in nature and not essential to intravascular clotting, it is logical to conclude that rapidly acting anticoagulants such as heparin should be administered over a longer period than previously was supposed necessary, in order to allow an adequate time for the prothrombin concentration to fall to therapeutic levels. It would seem that the prothrombin concentration is a more accurate guide than prothrombin time for the calculation of dosage of the coumarin-type anticoagulants.

3. Patients whose prothrombin has been excessively lowered by anticoagulants bleed most frequently from the urinary tract. Second and third in order of frequency as sites of bleeding are the gastrointestinal tract and the skin. Patients who bleed from any one of these areas and whose prothrombin concentration is greater than 10 per cent of normal should be examined carefully for an obscure lesion responsible for

the hemorrhage. In this series, an asymptomatic adenocarcinoma of the rectosigmoid was the site of bleeding in a patient whose prothrombin concentration was 20 per cent of normal.

4. In those patients who have an otherwise normal clotting mechanism, excessive prolongation of the Quick time is not usually associated with hemorrhage during the early phase of anticoagulant therapy unless the prothrombin concentration concomitantly falls below 10 per cent of normal.

5. Approximately two-thirds of the patients on long term anticoagulant therapy had a therapeutic reduction of prothrombin concentration when the Quick prothrombin time was less than twice the control value.

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Relation between Pain and Fatigue in Contracting Ischemic Muscle*

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WHEN a muscle is contracted repeatedly while its blood flow is restricted, a localized deep pain is experienced.[1] When the load against which the muscle is working is great, the pain quickly becomes so marked that cessation of the exercise is forced.[2] A light load results in less severe pain and the exercise can be continued for a longer period, but a localized muscular fatigue develops which brings the exercise to an end.[3] Painful syndromes may also occur in tissues with smooth muscles; thus, atherosclerotic narrowing of the superior mesenteric artery may be associated with "intestinal angina."[4]

One of the obstacles in the study of pain and fatigue is the subjective character of these phenomena.[5] Since psychogenic factors modify the perception and evaluation of symptoms, many investigators have been dissuaded from the examination of these problems. However, reproducible data on the phenomena of pain and fatigue can be obtained under controlled conditions, as indicated herein.

Zak[1] first suggested that the pain which follows exercise of a limb while a tourniquet obstructs its blood supply is similar to that of intermittent claudication. This intermittent claudication was early attributed to arterial spasm[6] since the pedal pulses in some patients disappear during exercise at approximately the time of development of pain. However, diminution of the peripheral pulses is a normal response to exercise which results from a rapid flow of blood through widely dilated arterioles, in the absence of pain.[7–10] In fact, Lewis et al.[2] found the inflow into a limb following the removal of a tourniquet to be greatly in excess of normal, even with the first beat following re-establishment of the blood flow.

The rate of development of pain is proportional to the product of the load per stroke and the number of contractions.[2] Ischemia without exercise did not significantly shorten the period before onset of pain during the subsequent exercise test. Variations in the rate of contraction have relatively little effect,[2] although McArdle and Verel[3] found that more work could be done before the onset of pain at rapid rates of contraction than at slow rates.

Lewis[2] postulated that a substance (P) produced during the contraction of an ischemic muscle diffuses into the extracellular spaces where it stimulates pain fibers. The possibility that the mechanisms that produce pain and fatigue are similar has also been suggested.[3]

We have re-examined some of the relationships between pain and fatigue production in ischemic muscle in man.

GENERAL METHODS

Thirteen clinically healthy men, twenty to forty years of age, were studied. The subject lay in a supine position on a plinth. The arms were elevated on armrests at an angle of approximately 20 degrees to eliminate venous congestion. Blood flow to the forearm was arrested by sudden inflation of a sphygmomanometer cuff on the upper arm to a pressure higher than systolic, about 230 mm. Hg. The subject then performed gripping contractions of the hand at rates of ten, twenty, forty or eighty movements per minute, rhythm being maintained with the aid of a metronome. No additional work load was applied.

The subjects were instructed to indicate the onset of pain in the arm. The pain increased steadily in intensity as the exercise was continued. However, localized fatigue usually caused the subject to stop the movements before severe pain developed. A single test on each arm was performed each day. The experiment was repeated five times at each of

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TABLE I
Relationship between Number of Contractions before Pain (P) and Fatigue (F)

Subject	Contractions Per Minute							
	10		20		40		80	
	P/F	Per Cent	P/F	Per Cent	P/F	Per Cent	P/F	Per Cent
1	53/68	78	61/87	70	53/72	74	64/77	83
2	60/93	65	75/110	68	65/101	64	64/101	63
3	27/64	42	48/108	45	58/129	45	65/120	54
4	26/45	58	31/61	51	42/71	59	54/82	66
Average	42/68	62	54/91	60	55/93	59	62/94	66

the indicated speeds arranged in a random order, for a total of twenty tests in each subject.

Three series of experiments were performed:

Basal. To establish baselines, the rate of development of pain and fatigue was examined in four subjects.

Preliminary ischemia. The influence of preliminary arrest of blood flow for 5 or 9 minutes prior to the exercise period on the time of occurrence of pain and fatigue was studied in four subjects at gripping rates of ten and eighty per minute.

Rate of recovery. The rate of recovery from pain and fatigue was studied in five subjects. Gripping movements were first performed under basal conditions until pain and fatigue developed. The cuff pressure was then dropped quickly to atmospheric levels to allow resumption of blood flow for 2, 8 or 64 seconds. The blood flow was then again obstructed by raising the cuff pressure quickly to 230 mm. Hg. The exercise was repeated and the performance was compared to that of the immediately preceding basal period.

RESULTS

Basal Data: The data of this group are given in Table I. The number of contractions before onset of pain or fatigue are reported separately for the four frequencies used. At frequencies of eighty per minute, the number of contractions of all the subjects approached a common mean value (Table I). No significant difference was observed between the number of contractions in the right or left arm.

Table I demonstrates that the ratio of the number of contractions before pain or fatigue (P/F) was relatively constant for each subject and was independent of the frequency of contraction.

Preliminary Ischemia: To reduce the oxygen available in the arm prior to the test exercise, blood flow to the arm was occluded by setting the cuff pressure at 230 mm. Hg. After the cuff had remained inflated for 5 or 9 minutes, the subject performed the gripping movements. The prolonged arrest of blood flow had no consistent effect on the number of contractions before onset of pain and fatigue in the succeeding exercise period (Table II). The pain/fatigue ratio was not significantly altered.

The number of contractions was significantly greater at eighty than at ten per minute, perhaps because the much longer period of occlusion of blood flow at the latter rate contributed to the discomfort and caused the subject to call a halt to the test.

Rate of Recovery: The number of contractions which could be performed immediately after transitory re-establishment of the circulation increased consistently with the duration of the period of restitution of blood flow. The ratios of recovery for fatigue and for pain were essentially similar (Fig. 1). After the brief period of 2 seconds of restitution of blood flow, the subjects were able to contract the fist about 20 per cent of the basal values before the return of pain or fatigue. After 8 seconds of restored blood flow, the recovery was about 30 per cent, and after 64 seconds of blood flow the recovery was about 65 per cent.

The similarity in the rates of recovery from pain and fatigue during resumption of flow supports the thesis that the mechanisms of production of these two symptoms are related.

COMMENTS

Although pain is a subjective phenomenon, it can be studied objectively. Variations from subject to subject in the time before pain may be

TABLE II
Number of Contractions* before Pain (P) and Fatigue (F), and the Ratio P/F*

Subject	Frequency	Control			5 Minutes			9 Minutes		
		P	F	P/F	P	F	P/F	P	F	P/F
5	10/min.	54	103	0.51	50	88	0.57	45	92	0.49
6		23	63	0.37	16	49	0.33	20	43	0.46
7		39	60	0.65	32	49	0.65	30	43	0.70
8		22	30	0.73	23	37	0.62	24	43	0.56
5	80/min.	67	89	0.75	69	100	0.69	64	99	0.65
6		35	80	0.44	36	73	0.49	30	67	0.45
7		67	100	0.67	57	97	0.60	51	85	0.60
8		64	88	0.73	48	76	0.63	37	64	0.58

* Each number is the average of five trials.

considered to represent subjective judgments of a self-selected degree of pain. As with pain, fatigue has its subjective components but the loss of strength of contraction can be observed and recorded.

The consistency of the ratio of the number of contractions before onset of pain and of fatigue for each subject suggests that these symptoms may share similar mechanisms. Thus, the pain/fatigue ratio in a given subject was unaffected by the frequency of contraction or by a preliminary period of ischemia; furthermore, the rates of recovery of the two symptoms remained unchanged following transitory reinstitution of blood flow.

If the process producing pain were related to the production of a substance P, this product of ischemic metabolism must be related directly to the sum of the tension generated by the muscle during the period of arrested blood flow.

The absence of pain during ischemia while the muscle is at rest suggests that the quantity of P factor produced during rest is minimal. After prolonged arrest of blood flow, the number of contractions before pain is practically identical with the number necessary if contractions are started at once (Table II). Since the oxygen available in the arm is reduced during the preliminary ischemia, the process producing P would appear to be relatively uninfluenced by a reduction of available oxygen. An anaerobic process is thereby suggested for production of P factor. The quantity of P produced is probably related to the sum of the tension produced by the recurrently contracting ischemic muscle.

Nociceptor fibers probably do not enter muscle cells; P must therefore first diffuse from

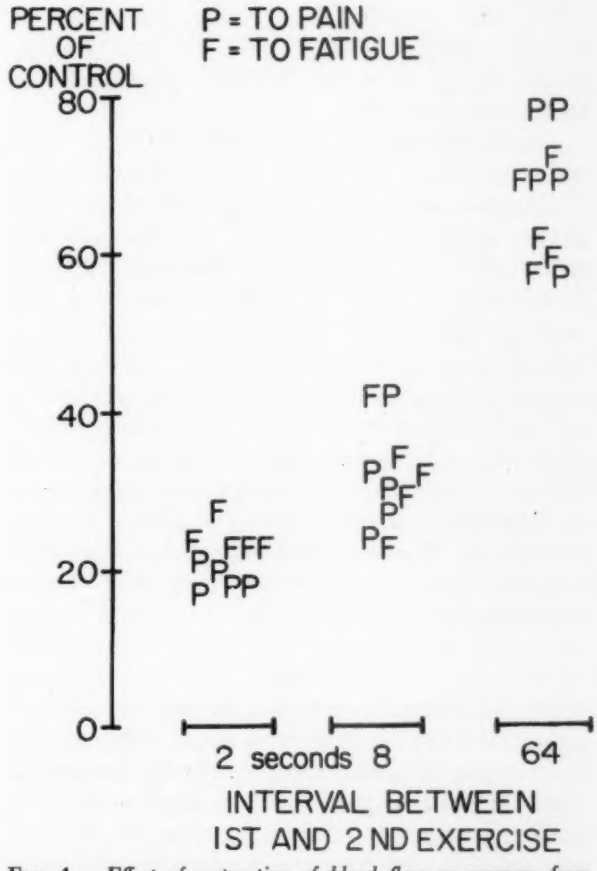


FIG. 1. *Effect of restoration of blood flow on recovery from "latent pain."* The control number of gripping contractions prior to onset of pain (P) and fatigue (F) in five trials at eighty per minute in each of four subjects was set at 100 per cent. The cuff pressure was then dropped to atmospheric values for 2, 8 or 64 seconds, following which the cuff was reinflated and the exercise repeated. The number of contractions before pain (P) and fatigue (F) during the second exercise is shown as per cent of that subject's control value. Recovery averages 20 per cent after 2 seconds of resumption of blood flow, about 35 per cent after 8 seconds, and about 70 per cent after 64 seconds.

the muscle to the interstitial spaces where, in sufficient concentrations, it may stimulate pain fibers.[2]

The sensation of pain disappears immediately on restoration of blood flow. P factor would therefore appear to be eliminated from the capillaries and the immediately adjacent tissue spaces with the first flush of blood. However, a latent pain persists even after one minute of unrestricted flow, as shown by the early appearance of pain and fatigue during the immediately succeeding round of ischemia and exercise. Since the latency disappears very gradually, it may be concluded that P factor diffuses relatively slowly, perhaps because it is a relatively large molecule. Extrapolation suggests that recovery would be complete in about 10 minutes. The reactive hyperemia following ischemic exercise has a similar time course, suggesting a similarity between pain and the vascular mechanism.

The potential biologic significance of the P factor deserves comment. Forced continuation of muscular work after development of pain and fatigue associated with a presumptive accumulation of P factor may produce deleterious effects. Nociceptors in the interstitial tissues of the muscles apparently utilize pain and fatigue signals to warn the central nervous system of a rising local concentration of specific metabolic end products, thereby preventing the development of undesirably high concentrations of P factor. If urgency demands that the exercise be continued beyond the point of pain and fatigue, or if these sensations are obtunded, excessive concentrations of the P factor may then bring about local injury.

Summary

The relationship between the development of pain and fatigue was studied in the rhythmically contracting ischemic muscles of the forearm of man. Localized pain develops after a relatively constant number of contractions in a given subject, followed by fatigue and an inability to continue the exercise. The ratio of the number of contractions prior to pain and to fatigue was essentially similar in each subject. The rate of contraction had little effect on these values, although rapid rates of contraction gave the more consistent results. Prolonged obstruction of blood flow to the arm prior to exercise had no consistent effect on the number of contractions or on the ratio. Recovery is only partial after resumption of blood flow for 2, 8 or 64 seconds since pain and fatigue reappear after fewer contractions than are required in the completely recovered state. Recovery is probably complete in about 10 minutes.

The results support the concept of Lewis[2] that a P factor produced in contracting ischemic muscle diffuses to the extracellular space where it stimulates pain fibers. Fatigue appears to share the same mechanism. On resumption of blood flow, P factor is presumptively washed from the site; it may persist as "latent pain," for up to about 10 minutes, becoming manifest as a decrease in the number of contractions which can be performed before pain during a subsequent ischemic period.

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Experimental Study

An Experimental Study of the Electrocardiographic Effects of Localized Myocardial Lesions*

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The mechanism by which the QRS complex is altered by myocardial infarction is not completely understood. It is probable that loss of excitable tissue and an abnormal excitation sequence in uninvolved portions of the myocardium are the major factors but their separate roles have not been clearly defined.

Abnormal Q waves as a manifestation of infarction are explicable on the basis of localized tissue loss in appropriate areas. It is likely, however, that tissue loss in certain areas results in different alterations of the QRS complex. Horan et al.[1] reported alterations of the mid-temporal and terminal portions of the QRS by extensive subepicardial lesions. Theoretic studies[2] suggested that tissue loss in many locations might be expected to alter the QRS complex without producing "pathologic" Q waves. Since considerable reliance is placed on such Q waves in current electrocardiographic interpretation, it is desirable that the effects of tissue loss be more precisely defined.

Gross conduction disorders such as bundle branch block are well-known occurrences in myocardial infarction. It is possible that less marked alterations of the ventricular excitation sequence are even more common. Such alterations have been suggested[3,4] on the basis of clinical electrocardiographic findings. Direct demonstration of disordered intramural excitation in experimental infarction has been reported.[5] The electrocardiographic effects of these disorders may prove to be useful in the recognition of infarction, or in some instances may make the diagnosis more difficult by obscuring the effects of tissue loss. In either event, more detailed definition of the role of conduction disorders in the electrocardiographic effects of infarction is desirable.

The purpose of this study was to examine alterations of the QRS complex produced by experimental myocardial lesions in dogs and to compare these with effects predicted on the basis of localized tissue loss. This comparison provided a basis for identifying those effects which were not the result of simple loss of excitable tissue but were likely to be the result of conduction disorders. Chemically produced lesions rather than actual infarcts were studied to eliminate the necessity for thoracotomy with its complex electrocardiographic effects. A system of electrode placement appropriate for the dog was employed to minimize those differences in the canine and human electrocardiogram that might result from the same electrode system applied to both.

Materials and Methods

Mongrel dogs in the weight range of 9 to 13 kg. and anesthetized with pentobarbital, 30 mg./kg.,

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were used in these experiments. Tracheotomy and artificial respiration were performed to eliminate the possible electrocardiographic effects of changing lung volume during the experiments. Localized myocardial lesions were produced by the injection of 0.1 to 0.3 cc. of 40 per cent formalin solution with a 20 gauge needle introduced through the chest wall. A small amount of malachite green, hematoxylin or India ink was mixed with the formalin to stain the lesion. Myocardial lesions were produced in twenty-three experiments. In eleven experiments the attempt to produce a lesion was unsuccessful.

Electrocardiographic Lead System: Three electrocardiographic leads were recorded simultaneously at a paper speed of 50 mm. per second using an orthogonal lead system designed for the dog.[6] The approximate center of the heart was considered to be a point on the midsternal line two intercostal spaces above the level of the maximal cardiac impulse determined by palpation. Three electrodes were placed on the anterior chest, each being 6 cm. from the cardiac center and located in the form of an equilateral triangle with the base located caudad. A single electrode was placed on the back directly opposite the point considered the cardiac center. Two electrodes were placed on each side of the chest a third the distance between anterior and posterior chest walls, with one 3 cm. cephalad and one 3 cm. caudad to a line drawn around the thorax and passing through the cardiac center. Other electrodes were placed on the left side of the neck and on the left leg.

Each electrode on the anterior chest wall was in series with 100,000 ohms resistance and each of those on the lateral chest walls and the neck was in series with 33,000 ohms resistance. The horizontal (X) component of cardiac electrical activity was recorded between the two pairs of electrodes on the lateral chest wall with a 100,000 ohms resistance in parallel with the galvanometer. The vertical (Y) component was taken between the neck and left leg electrodes. Anteroposterior (Z) cardiac electrical activity was recorded between the three anterior wall electrodes and the single electrode located on the back. Upward deflections represented relative positivity of the left electrodes in lead X, the leg electrode in lead Y and the back electrode in lead Z.

Records were obtained prior to insertion of the needle, with the needle in place, during or immediately after the injection of formalin, and at 10 minute intervals after the injection for periods up to 3 hours. In all but one experiment the contour of the QRS complex was stable for at least 20 minutes prior to termination of the experiment. One animal died in cardiac standstill 20 minutes after the injection of formalin.

Identification of Myocardial Lesions and Estimation of Tissue Loss: After the experimental period the hearts were removed and formalin fixed. With the heart in the approximate anatomic position, sections were made at uniform 3 mm. intervals using a plastic chamber with rigid guides for the cutting blade. The gross stained lesions were identified, their locations noted, and photographs of sections containing lesions were obtained. Microscopic sections of three lesions and surrounding cardiac muscle indicated that microscopic evidence of muscle damage was confined to the stained zone.

The theoretic electrocardiographic effects of localized tissue loss were estimated for each of the lesions. This estimate was based on the ventricular excitation sequence reported by Scher and Young[7] and on previously reported theoretic studies[2] in which the effect of localized tissue loss on records derived from this sequence was determined. The experimental control records showed a range of normal variability and the form of the QRS complex was never exactly the same as that derived from the reported excitation sequence. For these reasons it appeared that a qualitative estimate of the expected alterations due to tissue loss would be as informative as detailed derivation of these effects. Such a qualitative estimate of the probable effects of tissue loss in the area of each of the lesions was made. These predicted effects were compared with the electrocardiographic findings which occurred with the experimental lesions, and those which could not be reasonably accounted for on the basis of tissue loss were noted. The QRS alterations which occurred later than those which could be accounted for on the basis of tissue loss were considered to be probable effects of conduction disorders.

Results

ECG changes in absence of myocardial lesions

There was no significant alteration of the QRS complex in six of eleven experiments in which no gross myocardial lesion was produced. In two experiments there was decreased amplitude of Q and R waves in the anteroposterior (Z) lead and in one experiment there was decreased amplitude of the R wave only in this lead. In one experiment slightly decreased amplitude of a Q wave in the vertical (Y) lead occurred, and there was decrease in the amplitude of the R wave in the horizontal (X) lead in the other experiment. The mechanism of these alterations is not certain, but it is likely they were secondary to intravascular formalin. Similar effects cannot be excluded in the experiments with lesions although it is probable that less formalin entered the vascular system when a gross myocardial lesion was produced. The possibility of electrocardiographic alterations

TABLE 1

Summary of Electrocardiographic Effects of Localized Myocardial Lesions*

1. Transmural basal lesion resulted in larger Q waves in leads X and Y and smaller R waves in lead Y attributable to subendocardial and intramural tissue loss in lateral and inferior walls, respectively. Smaller S waves in lead Y are attributable to subepicardial basal tissue loss.
2. Transmural apical lesion resulted in decreased amplitude of R waves in leads X, Y and Z attributable to tissue loss in lateral, inferior and posterior walls, respectively.
3. Intramural and subendocardial lesion in mid-portions† of lateral and anterior walls and septum resulted in decreased amplitude of R waves in lead X and loss of "septal" Q wave in lead X, both attributable to tissue loss.
4. Intramural lesion near the apex in lateral and posterior walls resulted in decreasing amplitude of R waves in leads X and Z attributable to tissue loss.
5. Intramural apical lesion in anterior wall resulted in decreased amplitude of R waves in lead Z attributable to tissue loss.
6. Intramural lesion in mid-portions† of posterior and inferior walls resulted in increased amplitude of Q waves in lead Z and decreased amplitude of R waves in lead Y attributable to tissue loss.
7. Intramural lesion in mid-portions† of lateral wall resulted in Q waves in lead X attributable to tissue loss.
8. Transmural lesion in mid-portions† of lateral, inferior and posterior walls resulted in deeper Q waves in lead X and decreased amplitude of R waves in leads Y and Z attributable to tissue loss in these areas.
9. Transmural lesion in mid-portion† of right ventricle resulted in smaller Q waves in leads X and Z attributable to tissue loss.
10. Subendocardial lateral wall lesion near the apex resulted in decreased amplitude of R waves in lead X attributable to tissue loss. Increased amplitude of S waves in lead Y and decreased amplitude of R waves in lead Z suggested disordered conduction.
11. Subendocardial and intramural lesion in mid-portions† of lateral and inferior walls resulted in decreased amplitude of R waves in leads X and Y attributable to tissue loss. Increased amplitude of late S waves in lead Y suggested disordered conduction.
12. Intramural lesion in mid-portions† of anterior wall and interventricular septum resulted in decreased amplitude of Q waves in lead Z and larger R waves in lead Y attributable to tissue loss. Decreased amplitude of R waves in lead Z suggested disordered conduction.
13. Intramural lesion in lateral wall near the apex resulted in larger Q waves in lead X attributable to tissue loss. Replacement of a late S wave by an R wave in lead X suggested disordered conduction.
14. Subendocardial lesion in mid-portions† of lateral and anterior walls and interventricular septum resulted in larger Q waves in lead X and increased amplitude of R waves in lead Z attributable to tissue loss. Increased amplitude of late portions of R waves in lead Z suggested disordered conduction.
15. Subendocardial apical lesion in inferior and anterior walls resulted in decreased amplitude of R waves in lead Y and decreased amplitude of Q waves in lead Z attributable to tissue loss. Decreased amplitude of late R waves in lead Z suggested disordered conduction.
16. Subendocardial and intramural lesion in mid-portions† of lateral, inferior and anterior walls and interventricular septum resulted in decreased amplitude of R waves in leads X and Y and decreased amplitude of Q waves in lead Z attributable to tissue loss. Decreased amplitude of late R waves in lead Z suggested disordered conduction.
17. Intramural lesion in mid-portions† of lateral and anterior walls and interventricular septum resulted in decreased amplitude of R waves in lead X and decreased amplitude of Q waves in lead Z attributable to tissue loss. Decreased amplitude of S waves in lead Y and loss of S waves in lead Z suggested disordered conduction.
18. Subendocardial lesion in mid-portions† of anterior wall and interventricular septum resulted in decreased amplitude of Q waves in lead Z and increased amplitude of early portions of R waves in lead X attributable to tissue loss. Decreased amplitude of late R wave in lead Z suggested disordered conduction.
19. Subendocardial and intramural lesion in mid-portions† of lateral and anterior walls and interventricular septum resulted in increased amplitude of Q waves and smaller R waves in lead X and decreased amplitude of Q waves in lead Z attributable to tissue loss. Decreased amplitude of late R wave in lead Z suggested disordered conduction.
20. Subendocardial and intramural lesion in mid-portions† of lateral wall resulted in increased amplitude of Q waves in lead X attributable to tissue loss. Decreased amplitude of late S waves in lead Y suggested disordered conduction.

* All lesions are left ventricular unless otherwise stated.

† The term "mid-portions" is used with reference to the apex to base axis of the heart.

by factors other than the gross lesions complicates the correlation of lesion location and size with electrocardiographic findings, but it should be noted that similar complicating factors might also occur with other modes of lesion production. Even with actual myocardial infarction, secondary factors such as shock and altered autonomic tone may be responsible for some electrocardiographic changes. In the present series of experiments in which gross areas of myocardial destruction were produced and in which QRS changes which could be reasonably attributed to tissue loss almost always occurred, it seems likely that

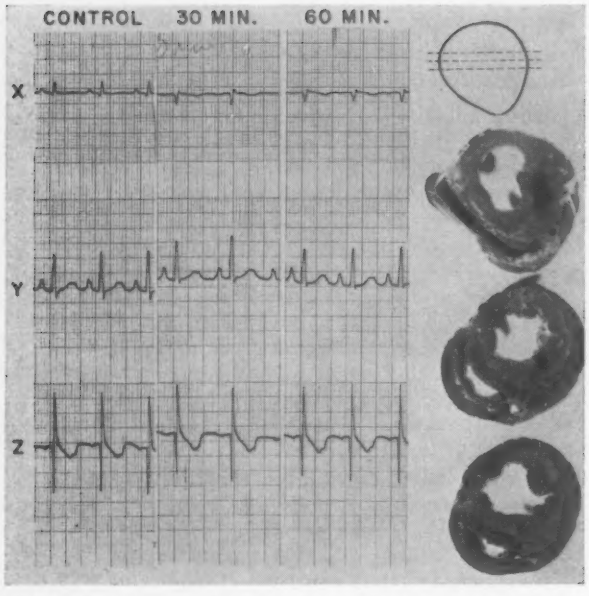


FIG. 1. Electrocardiograms recorded from an orthogonal lead system applied to a dog. The control record was obtained with a 20 gauge needle inserted in the left ventricular wall, and the other records shown were obtained 30 and 60 minutes after the injection of 0.2 cc. of 40 per cent formalin solution. The resulting lesion in subendocardial and intramural portions of the lateral left ventricular wall is shown in the cardiac sections which were taken at the approximate levels indicated in the diagram over the sections. The major electrocardiographic alterations occur in lead X and consist of a wide deep Q wave and decreased amplitude of the R wave. These alterations are attributable to tissue loss in the area of the lesion.

the major alterations of the QRS complex were direct results of the lesions.

ECG CHANGES PRODUCED BY MYOCARDIAL LESIONS

The changes in the QRS complex which occurred in association with lesions were divided into those which could be attributed to tissue loss and those which could be accounted for on the basis of conduction disorders. Nine of the twenty-three lesions resulted in QRS changes which could be attributed wholly to tissue loss (Table 1, 1 to 9). Eleven lesions were associated with some QRS alterations which could be accounted for on the basis of tissue loss and, in addition, other effects on the QRS complex which could be reasonably attributed to a disordered ventricular excitation sequence in portions of the myocardium not involved by the lesions (Table 1, 10 to 20). Three lesions were not associated with definite changes in the QRS complex, and in three other experiments some of the QRS alterations could not be attributed to either tissue loss or conduction disorders.

Effects of Localized Tissue Loss: Twenty of the twenty-three lesions resulted in changes in the QRS complex which could be attributed to this factor. These included lesions confined to the subendocardial half of the myocardium. The specific alterations were dependent on the location and extent of individual lesions.

Subendocardial and intramural lesions in the lateral wall resulted in the occurrence of Q waves or decreased amplitude of R waves in lead X. Seven lesions which did not extend to the epicardial surface of the heart were confined to the lateral wall and three others extended into this wall and resulted in the QRS alterations noted previously. Four of these lesions were restricted to the inner half of the myocardium. A subendocardial and intramural lesion in the lateral wall and the resulting electrocardiographic effects are shown in Figure 1.

Four subendocardial and/or intramural lesions extending into the diaphragmatic wall of the left ventricle were associated with decreased amplitude of the R waves or the development of Q waves in the Y lead. One of these lesions was confined to the subendocardial half of the ventricular wall and the other three were restricted to the inner two-thirds of the wall.

Anterior wall lesions confined to the subendocardial and/or intramural portions resulted in decreased amplitude or loss of the Q wave in lead Z which normally reflected excitation directed anteriorly. Three lesions confined to and three lesions extending into this portion of the heart were produced. Two of these lesions were confined to the inner half of the cardiac wall.

Only one intramural lesion which extended into the *posterior wall of the left ventricle* was produced. This lesion was confined to the middle third of the ventricular thickness and resulted in increased amplitude of the normal Q wave in lead Z.

Only four lesions in this series were *transmural*. Three of these resulted in QRS complex changes which could be entirely attributed to tissue loss and one also resulted in evidence of disordered excitation. Two lesions involved the *inferior and basal posterior walls* of the left ventricle. These lesions were associated with alterations of the terminal portion of the QRS complex as would be expected on the basis of tissue loss in an area normally activated late in the process of ventricular excitation. Both lesions resulted in decreased amplitude of S waves in lead Y and

decreased amplitude of R waves in lead Z. These lesions also involved the lateral wall, and abnormal Q waves and decreased amplitude of R waves in lead X attributable to tissue loss in this location occurred. Interpretation of the significance of changes in the terminal portion of the QRS complex resulting from lesions in areas normally activated late in ventricular excitation presents a special problem. Such alterations would be expected on the basis of tissue loss alone; however, the identification of conduction disorders in this study was based on the occurrence of QRS alterations in later portions of the complex than could be accounted for by tissue loss. The only other basis for identification of conduction disorders was the occurrence of QRS changes whose direction could not be accounted for by tissue loss in the area of the lesion. The transmural lesions whose effects are being described resulted in alterations of the QRS complex which were appropriate for tissue loss; however, conduction disorders cannot be excluded as the basis of the alterations of the terminal portion of the QRS complex.

One transmural lesion involving anterior and lateral left ventricular walls also extended into the interventricular septum. This lesion resulted in loss of the normal Q wave in lead X which could be attributed to tissue loss in the septum and decreased amplitude of the peak of the R wave in leads X and Z which could be attributed to tissue loss in lateral and posterior walls. There were no definite alterations in the form or direction of the terminal portion of the QRS complex. Such alterations would not be expected on the basis of tissue loss in the areas named even with a transmural lesion.

The other transmural lesion was located near the apex and involved lateral, inferior and anterior left ventricular walls. Tissue loss in these areas was reflected by decreased amplitude of the R wave in leads X and Y and by decreased amplitude of the normal Q wave in lead Z. There was also a definite decrease in the amplitude of the R wave in lead Z with a change in configuration of its downstroke. This could not be accounted for on the basis of tissue loss since activation of the apical regions including the subepicardial portion is normally completed prior to the terminal portion of the QRS complex. The change described was, therefore, considered evidence of altered excitation in uninvolved portions of the myocardium.

Three lesions were restricted to the *free wall of the right ventricle*. Two of these did not result in recognizable alterations of the QRS complex and will be mentioned in a later section. One right ventricular lesion near the apex resulted in decreased amplitude of the normal Q wave in lead X, suggesting that in this instance normal activation of the right ventricular wall contributed to the occurrence of this wave.

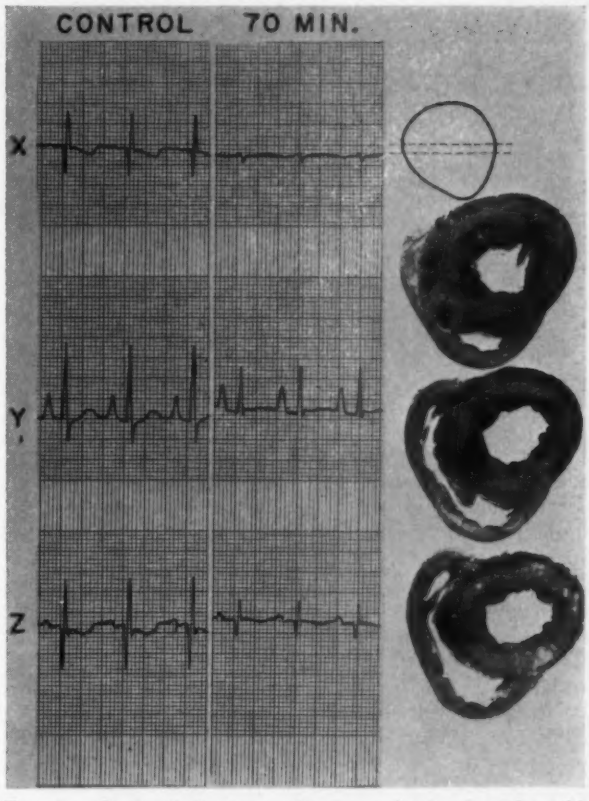


FIG. 2. Control electrocardiogram obtained with a 20 gauge needle in the interventricular septum and record obtained 7 minutes after injection of 0.2 cc. of 40 per cent formalin solution at that site. The two lower cardiac sections at the approximate level of the dotted lines in the diagram show a localized lesion confined to the interventricular septum, while the upper cardiac section contains small linear streaks of the formalin-dye solution but does not show a confluent localized lesion. The electrocardiograms demonstrate loss of the septal Q wave which can be attributed to tissue loss and alterations of the terminal portion of the QRS complex which were interpreted as evidence of a conduction disorder.

Eight lesions extended into and one was confined to the *interventricular septum*. Evaluation of the effects of tissue loss in this area was difficult, since in several instances the expected effects of the septal lesion tended to oppose the expected effects of the free wall lesion. For example, certain septal lesions might be expected to decrease the amplitude of the initial normal Q wave ("septal Q") in lead X, but if the lesion also involved the lateral cardiac wall an increase

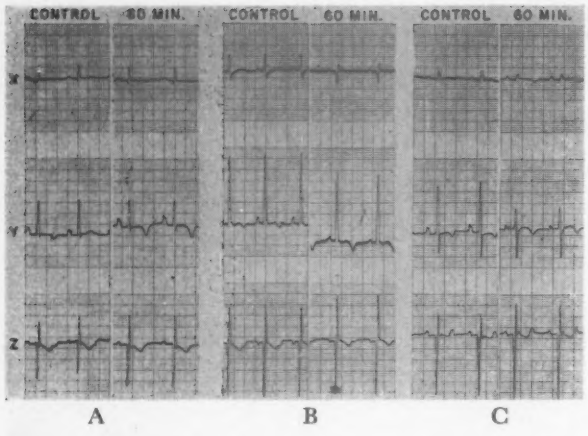


FIG. 3. Electrocardiograms recorded before and after production of localized myocardial lesions in dogs. The control records were obtained with a needle inserted into the myocardium at the site where 0.2 cc. of 40 per cent formalin solution was later injected. A, decreased amplitude of the R wave in lead Y which was the result of an intramural lesion confined to the inferior cardiac wall and could be accounted for solely on the basis of localized tissue loss. B, deep wide Q waves in lead X which were the result of an intramural lesion of the lateral wall and can be accounted for on the basis of tissue loss. There is also an alteration of the terminal portion of the QRS complex with the S wave in the control lead X being replaced by an R wave in the record 60 minutes after formalin injection. This alteration was interpreted as evidence of a conduction disorder producing effects opposite in direction to those resulting from tissue loss. C, decreased amplitude of the R waves in leads X and Y which resulted from tissue loss in the subendocardial and intramural portions of the lateral and inferior cardiac walls. There is also an increased amplitude of the S waves in lead Y which could not be attributed to tissue loss in the area named and was interpreted as evidence for a conduction disorder producing effects in the same direction as those of tissue loss.

in amplitude of the Q wave could occur. In this study recognizable evidence of septal tissue loss occurred in four of the nine lesions. Loss of "septal Q waves" occurred in two experiments. This effect of septal lesions in man has been reported by Burch.[8] One lesion of the left side of the septum resulted in increased amplitude of R waves in lead X, while one lesion of the inferior portion of the septum was associated with increased amplitude of the R wave in lead Y. The lesion which was confined to the septum and its electrocardiographic effects are illustrated in Figure 2. This lesion resulted in loss of the "septal Q wave" which can be attributed to tissue loss and also gave evidence of disordered intraventricular conduction.

Conduction Disorders: In addition to QRS changes which could be attributed to localized tissue loss, eleven lesions resulted in alterations which could be accounted for on the basis of conduction disorders. These alterations could be divided into two categories based on direction of the alterations relative to the direction of changes produced by tissue loss. (1) Two lesions resulted in changes explicable on the basis of disordered conduction with the alterations being in the same direction as those resulting from tissue loss. Both lesions were located in the subendocardial and intramural portions of the lateral wall. One lesion was located near the apex and the other approximately mid-way between apex and base. (2) In nine experiments changes attributable to disordered conduction were opposite in direction to those which could be ascribed to tissue loss. These lesions were all subendocardial and/or intramural and were all anterior, lateral or anterolateral in location. All lesions except one included involvement of the interventricular septum. This was in striking contrast to those lesions which did not result in conduction disorders by the standards of this study. In that group only one of the nine lesions involved the interventricular septum. Conduction disorders resulting in effects in the same and in the opposite direction to those of tissue loss are illustrated in Figure 3.

Effect of Needle Insertion into Myocardium: The most striking evidence that significant alterations of the ventricular excitation sequence may occur as a result of local lesions was the finding that the 20 gauge needle inserted into the myocardium sometimes grossly altered the form of the electrocardiogram. Such alterations occurred in five experiments in this study. In one of these the electrocardiogram was observed at intervals for 30 minutes with the needle in place and another 30 minutes after removal of the needle, and the new form of the record remained stable. No consistent pattern of changes was observed. Decreased amplitude of both Q and R waves in lead Z occurred in three experiments, increased amplitude of the Q wave in lead X occurred in two experiments, and decreased amplitude of the R wave in lead X, decreased amplitude of an S wave in lead X and loss of a small Q wave in lead Y each occurred in one experiment.

Lesions Not Associated with QRS Alterations: Three lesions did not result in perceptible alterations of the QRS complex. Two of these were restricted to the right ventricular wall, one

being transmural and extending over a vertical distance of nearly 2 cm., and the other being a small intramural right ventricular lesion near the base. In one other experiment a small subepicardial lesion in the posterior wall of the left ventricle near the apex was not associated with changes of the QRS complex.

QRS Alterations Which Could Not Be Attributed to Tissue Loss or Conduction Disorders: Such alterations occurred in three experiments. In all of these the lesions were located in lateral and posterior left ventricular walls, two being near the apex and one near the base. All were associated with decreased amplitude of the normal Q wave in lead X and one was associated with decreased amplitude of the normal Q wave in lead Z. These changes were opposite in direction to those expected on the basis of tissue loss. They also occurred early in the QRS complex so they could not be attributed to conduction disorders by the standards employed in this study. In these experiments, changes in later portions of the QRS complex consisting of decreased amplitude of the peak deflections of the R waves in leads X and Z were compatible with the expected effects of tissue loss in the area of lesions.

Comments

The usefulness of the electrocardiogram in the diagnosis of myocardial infarction is generally recognized, but it is well known that infarction may exist in absence of findings currently considered indicative of that lesion. Better understanding of the mechanism of electrocardiographic alterations in infarction may be a step toward improved recognition. For this purpose, experimental studies have certain advantages over clinicopathologic investigations. Control records can be obtained shortly before production of lesions in all instances. Some control of the size and site of the lesion can be exercised and more detailed description of these characteristics than is common in routine autopsy examination can be carried out. Experimental studies in dogs have the further advantage that the most detailed information available concerning the ventricular excitation sequence applies to this animal. These data can be employed, as they were in the present study, to estimate the expected effects of localized tissue loss and differentiate these from the effects of other factors. In this study use of an electrode system designed for the dog and production of lesions without thoracotomy eliminated two of the shortcomings of some previous experimental studies of myocardial lesions.

The study furnished evidence that localized lesions in the dog's heart usually alter the electrocardiogram in a manner consistent with that predicted on the basis of tissue loss applied to the ventricular excitation sequence reported by Scher and Young.[7] This included lesions restricted to the subendocardial half of the myocardium whose mode of excitation and influence on the form of the electrocardiogram have been disputed.[9] In some instances "pathologic" Q waves which would be recognizable as the result of a localized lesion by current standards of electrocardiographic interpretation resulted from such lesions.

The study also furnished evidence that altered ventricular excitation in uninvolved portions of the myocardium is a significant factor in the QRS alterations associated with localized myocardial lesions. Such alterations were identified by the standards employed in this study as occurring with more than half of the lesions produced. There was a striking correlation of these alterations with location of the lesion in the interventricular septum.

The majority of the QRS alterations attributed to conduction disorders were opposite in direction to those which occurred on the basis of tissue loss, but in two instances these factors resulted in changes in the same direction. The exact mechanism involved in the conduction disorders is not certain. Grant and Murray[4] reported evidence for conduction disorders in association with myocardial infarction which resulted in QRS alterations opposite in direction to those of tissue loss. They suggested that two major divisions of the left bundle branch might account for these findings and postulated that when one division was interrupted by a lesion, the surrounding area which was normally activated from that division become excited via a myocardial route from the other division. This mechanism need not be restricted to two divisions of the bundle branch and is a plausible explanation of conduction disorders associated with localized lesions. In most instances this mechanism might be expected to result in QRS alterations roughly opposite those due to tissue loss. It seems possible, however, that in some instances the mode of excitation in uninvolved muscle near a lesion might be largely self-cancelling so that QRS effects similar to those of more extensive tissue loss might occur.

The occurrence of the QRS alterations in

some of the experiments in which lesions were not produced and the failure to find recognizable QRS alterations by all of the lesions illustrate some of the shortcomings of the present study. It is difficult to exclude secondary factors which may alter the electrocardiogram from the experimental or clinical setting of gross myocardial lesions. Failure to find recognizable QRS changes associated with some of the lesions may reflect an inadequate display of electrocardiographic data in those experiments. The normal QRS duration in the electrocardiogram of the dog is approximately half that in records from human subjects. The recording paper speed of 50 mm. per second employed in this study may not have been rapid enough to demonstrate some significant changes in the contour of complexes. The failure to find significant increase in the duration of QRS complexes as a result of myocardial lesions should also be judged with reference to the paper speed employed.

Summary

Localized lesions were produced in twenty-three dogs by the injection of 40 per cent formalin into the myocardium through the intact chest wall. Simultaneous electrocardiographic leads from an orthogonal lead system designed for this animal were recorded before and after production of the lesions. The hearts were sectioned at 3 mm. intervals to demonstrate location of the lesions. The effects of localized tissue loss in each of these areas were qualitatively predicted on the basis of the ventricular excitation sequence in the dog. These predicted effects were compared with the actual effects of the lesions.

Twenty lesions resulted in QRS alterations similar to those predicted on the basis of tissue loss. These included some lesions restricted to the subendocardial half of the myocardium, and some of these were manifest by abnormal Q waves in the electrocardiogram.

Alterations of the QRS complex which followed those attributed to tissue loss occurred with eleven lesions and were considered to be probable results of conduction disorders. There was a definite correlation of conduction disorders and involvement of the interventricular septum by the lesions.

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Review

Myocardial Ischemia

Nature of Ischemic Electrocardiographic Patterns in the Mammalian Ventricles as Determined by Intracellular Electrographic and Metabolic Changes*

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THIS COMMUNICATION reports the results of investigations of some of the fundamental metabolic and bioelectric phenomena which appear to be responsible for various electrocardiographic patterns commonly observed in many different conditions characterized by myocardial ischemia.

It has been previously suggested that there are two general types of myocardial ischemia, a mild, diffuse type and a severe, localized form.[1-5] These two types appear to differ markedly not only in degree and usually in distribution but also in their pathophysiology and clinical manifestations. Furthermore, they produce electrocardiographic patterns which are in almost all instances different from one another. In many respects, the electrocardiographic changes characteristic of severe ischemia appear to be *opposite* to those of mild ischemia. It is indeed difficult to understand why different degrees of the same stress, i.e., ischemia, should cause such different clinical and electrocardiographic pictures. It is hoped that this communication will offer at least a partial explanation of this apparent paradox.

Both kinds of ischemia and their typically different electrocardiographic patterns have been observed clinically and have been reproduced experimentally.[1,2,3,5,6] As examples of severely ischemic clinical conditions we may consider the situation in the early phases of acute severe myocardial infarction and during the attacks of the variant form of angina pectoris.[1,4] The electrocardiographic findings in these conditions are very similar. They consist of primary elevation of the S-T segment, increase in amplitude of the R wave or the development of "giant" R waves,[4,6] and decrease or disappearance of the S wave. On the other hand, examples of clinical conditions in which "mild" ischemia† is present are as follows: (1) attacks of classic angina pectoris, (2) some cases of hemorrhagic shock[7] and (3) some cases of mild myocardial infarction.[8] The typical electrocardiographic findings in each of these conditions are very similar. They consist of primary depression of the S-T segment associated in some instances with decreased amplitude of the R

† It has been shown that in classic angina pectoris the ischemia is distributed in numerous "islands" on all surfaces of both ventricles.[2] The ischemia in each of these "islands" is mild. Thus when reference is made in this paper to the "mild" ischemia of classic angina pectoris, we are speaking of the ischemia in individual areas or "islands," not of the total "amount" of ischemia which is present in this condition. Because of the large number of "islands" of ischemia in classic angina pectoris, the total "amount" of ischemia may be as great or greater than in myocardial infarction, even though each "island" is only mildly ischemic.

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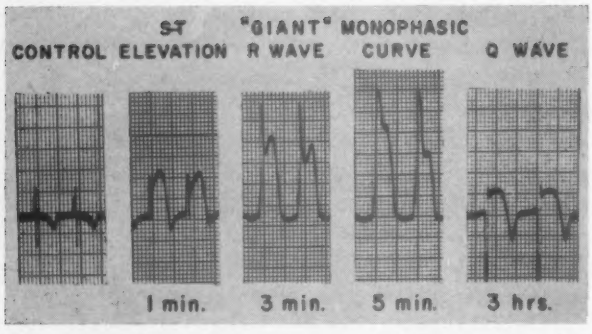


FIG. 1. Electrographic changes in direct epicardial lead following ligation of anterior descending branch of coronary artery. Note the appearance of S-T elevation, "giant" R wave and diminution of S wave.

wave and increased depth of the S wave. It should be emphasized that the S-T depression is primary and not reciprocal. The concept of primary S-T depression is in no way at variance with the principle of reciprocity[9] or the fundamental laws of electrocardiography. Because these different kinds of electrocardiographic changes had been observed clinically in ischemic conditions, the question arose whether a fundamentally different degree of ischemia might be responsible for each pattern. In order to investigate this possibility, a number of clinical and experimental studies were made. The results of these investigations, presented in previous communications,[3,5] indicate that there appear to be two different types of myocardial ischemia: a severe form producing S-T elevation, large R waves and small or absent S waves, and a mild form resulting in primary S-T depression, often with decrease in height of the R waves and increase in depth of the S waves. In order to determine the reasons for these remarkable electrocardiographic differences, various degrees of ischemia were produced experimentally by modifying the coronary circulation.

HEMODYNAMIC EXPERIMENTS

1. Severe Ischemia: In these experiments, a total of sixty dogs was used. Severe localized myocardial ischemia was produced by ligating a large branch of the left anterior descending coronary artery. The region supplied by the ligated artery became cyanotic, lost its contractility and demonstrated systolic ballooning. Direct leads were taken from various points over the severely ischemic area. In forty-seven trials elevation of S-T segments, increase in amplitude of the R waves (sometimes "giant" R waves) and decrease in depth or disappearance

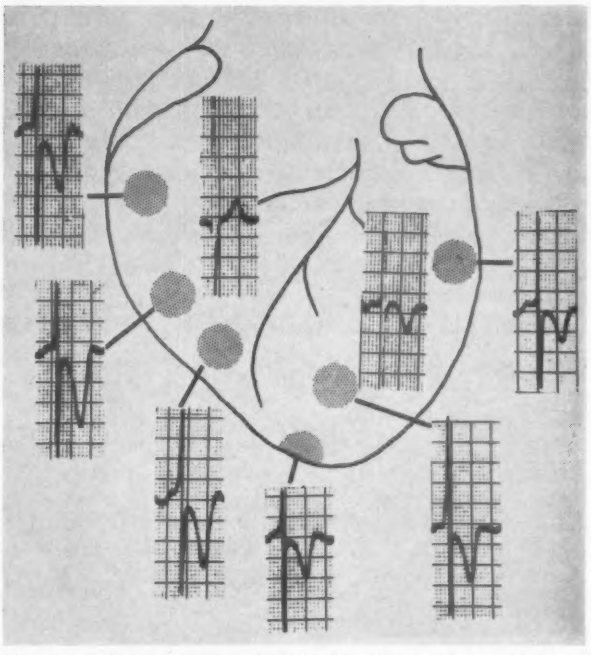


FIG. 2. Direct epicardial leads obtained at time of cardiac surgery in a patient with severe classic angina pectoris. Multiple "islands" of S-T segment depression, diagrammatically represented, are located over all aspects of both ventricles. The S-T segments are isoelectric between these "islands" of S-T depression. The appearance of the myocardium in these "islands" does not differ from that of the surrounding myocardium.[2]

of S waves[5] were consistently found (Fig. 1). In the central zone of large, severely ischemic areas, "giant" R waves were almost always found. As the exploring electrode was moved toward the periphery of such areas, the R wave became less and less markedly increased in amplitude until at the edge of the area, the difference from the normal amplitude was imperceptible.

2. Mild Ischemia: In contrast to these changes, it has been observed that the S-T segments are depressed in the standard leads in classic angina pectoris, the R wave sometimes becomes smaller and the S wave deeper. By studying direct epicardial leads of fifteen patients with this condition undergoing thoracic surgery,[2] it was revealed that the S-T depression of the clinical electrocardiogram was due to numerous "islands" of S-T depression on all surfaces of both ventricles interspersed with areas which showed normal tracings (Fig. 2). Similar S-T depressions may occur clinically after massive hemorrhage.[7]

In order to reproduce these findings experimentally, severe hemorrhagic hypotension was induced in eighteen dogs by slow bleeding. The systemic blood pressure was maintained at

an average level of 40 mm. Hg. Direct epicardial leads usually showed the same numerous islands of S-T depression,[2] often with loss of amplitude of the R wave and increased depth of the S wave.[6] These islands did not become cyanotic and could not be distinguished visually from the rest of the myocardium. These S-T changes closely resembled those in patients with classic angina pectoris.

3. Mild Ischemia at Border of Severely Ischemic Area: When an area of severe ischemia was produced in a dog by coronary ligation, as described, a tall R wave, elevated S-T segment and S wave occurred first and most markedly in the central part of this region. Soon after, but to a less marked degree, similar changes were recorded progressively from intermediate and peripheral portions of the ischemic area. After 15 to 20 minutes the periphery of this region became less cyanotic and the S-T segment recorded from this zone usually became depressed.[5] What may be the same phenomena has on occasion been observed in man after myocardial infarction—elevated S-T segments over the region of maximum ischemia, becoming less elevated as the electrode is moved away from this area, and actually depressed at the less ischemic border of the lesion.

4. Varying Degrees of Ischemia: In order to determine more accurately whether S-T elevation is characteristic of more severe ischemia than S-T depression, an area of myocardium was provided with a double blood supply which replaced the normal blood supply. Circuit 1, supplying the central part of this area, was obtained from the carotid artery through a catheter and circuit 2, supplying the periphery, from the femoral artery. When circuit 1 was tied off the central portion of this area became severely ischemic and S-T elevation was consistently recorded from its surface. Later, at its less ischemic margin as cyanosis lessened, S-T depression usually occurred. Now circuit 2, supplying this marginal region, was ligated, increasing the ischemia. Deep cyanosis reappeared in this area and S-T elevations promptly replaced the S-T depressions.[5] *Thus, as the ischemia increased, S-T elevation appeared where S-T depression had previously been present.*

Sixteen experiments were also performed to determine the effect of ligating a coronary artery and then releasing the tie.[5] While the ligature was tied, maximum ischemia was present in the central part of the affected area and the S-T segment became markedly elevated. The tie was then released, ischemia became less severe and after a few minutes S-T pepression sometimes occurred. Some minutes later, the ischemia usually disappeared and the S-T segment became isoelectric.[5] Thus with severe ischemia, S-T elevations were recorded. When less marked ischemia replaced the severe ischemia S-T depressions sometimes replaced the S-T elevations.

A similar sequence of events occurred in one case of the variant form of angina pectoris in which we were fortunately able to obtain electrocardiograms during an entire attack. At the height of the attack, when ischemic was intense, the S-T segment was elevated. As the pain and ischemia decreased, the S-T segment became lower and transiently *depressed* before returning to the isoelectric line.[6] These experiments and their clinical counterparts seem to suggest that severe and mild types of ischemia seem to produce practically opposite kinds of electrocardiographic changes.

In order to determine the fundamental factors responsible for the various electrocardiographic changes in these two kinds of myocardial ischemia several other series of experiments have more recently been carried out. These were designed to investigate both the bioelectric and metabolic changes occurring in severely and mildly ischemic myocardium, and to determine what role these changes might play in the genesis of the abnormal electrocardiographic patterns observed in these conditions.

Severe Ischemia

Bioelectrical Experiments: The bioelectrical changes resulting from severe myocardial ischemia produced by coronary occlusion were studied by investigation of the potential changes of individual cardiac cells as determined by the intracellular electrogram and its relation to the adjacent surface electrogram. In ninety-four experiments more than 1,000 intracellular penetrations were made with a microelectrode.[10] Simultaneous intracellular electrograms and overlying surface electrograms were recorded. A special technic was devised to prevent the electrode from being displaced by the motion of the heart.[10,12]

A direct-coupled amplifier was used in the electrocardiograph for recording both surface and intracellular electrograms.[11] This permits differentiation between true S-T deviation and apparent S-T deviation due to T-Q segment shift. After a microelectrode is placed within

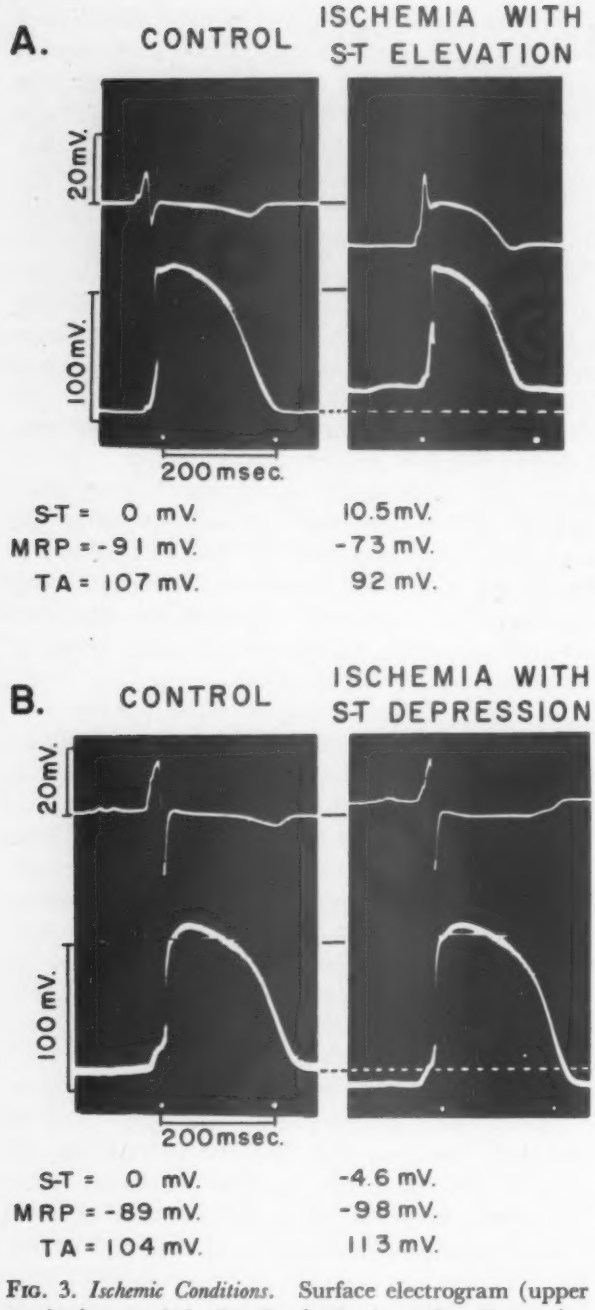


FIG. 3. *Ischemic Conditions.* Surface electrogram (upper tracing) recorded directly from the epicardium of a canine ventricle and intracellular electrogram (lower tracing) recorded simultaneously from underlying myocardial cell. ST = S-T segment deviation; MRP = membrane resting potential; TA = total amplitude of membrane action potential. A, recorded from severely ischemic areas produced by coronary artery ligation. Note decrease in negativity of membrane resting potential, T-Q segment depression (relative S-T elevation), increase in R wave amplitude and disappearance of S wave after coronary artery ligation. B, recorded from "mild" ischemic area with S-T segment depression produced by severe hemorrhagic hypotension. Note increase in membrane resting potential, T-Q segment elevation (relative S-T depression).

a single cell it will record, during the diastolic phase, a negative potential called the membrane resting potential.[13,14] This potential corresponds to the isoelectric level of the T-Q segment in the overlying surface electrogram. In normal cells of the mammalian ventricle[10] the membrane resting potential averages approximately −90 mv.

In the ninety-four experiments in which severe ischemia was produced by coronary artery ligation, the membrane resting potential consistently showed a *marked decrease in negativity*. This resulted in a proportional lowering of the T-Q segment in the surface electrocardiogram (Fig. 3A). This would appear as marked S-T elevation in the clinical electrocardiogram which does not maintain a constant isoelectric level.* Table 1A shows the quantitative findings in these experiments.

Metabolic Experiments: Because of the strong effects of potassium and sodium ions, on the transmembrane potentials of individual cells, the influence of these electrolytes on the intracellular and surface electrograms in ischemic myocardium was reinvestigated.

The K^+ and Na^+ concentration of the blood entering and leaving severely ischemic myocardium was determined in eighteen experiments.[15] In such areas in which S-T elevations were present, the potassium ionic concentration of the venous blood leaving the region was much higher than that of the arterial blood. However, the sodium ionic concentration of the venous blood was usually lower than that of the arterial blood. These findings indicate that in markedly ischemic myocardium the intracellular K^+ decreases and the Na^+ concentration most likely increases.[16,17]

These abnormalities are probably due to injury of the cells and their membranes, and to a partial inability of the cell membrane to maintain the normal ionic gradient between intra- and extracellular electrolytes. This imbalance results in a decrease in the transmembrane ionic gradient for both K and Na ions which is correlated with S-T elevation in severe ischemia.[18] The decrease in gradient may very well produce a state of hypopolarization by diminishing the charge on the membranes of the ischemic cells.

In order to determine whether these changes in the chemical pattern of the blood are at

* In severe, prolonged ischemia there may also occur an actual primary elevation of the S-T segment as determined with the aid of the direct-coupled amplifier.

TABLE I

Changes in Membrane Resting Potential (MRP), Overshoot of Intracellular Electrogram and Simultaneous Changes in S-T Level of Surface Electrogram

Data	No. of Trials	S-T Segment Deviation	MRP	Overshoot
*A. After Coronary Occlusion**				
Control	94	2.12 ± 0.12	89.4 ± 0.70	13.1 ± 0.41
After coronary occlusion	91	9.92 ± 0.36†	73.8 ± 0.51†	12.8 ± 0.45
After reopening	67	2.52 ± 0.43	84.5 ± 0.83	13.0 ± 0.48
B. During Perfusion of Nonischemic Myocardium with High K^+ (10 mEq./L. K^+ mixed with 142 mEq./L. Na^+)†				
Control	40	1.00 ± 0.32	92.0 ± 1.70	14.2 ± 1.48
Maximum effect of perfusion	40	6.31 ± 0.27†	80.3 ± 1.86†	13.6 ± 1.80
C. During Perfusion of Nonischemic Myocardium with Low Na^+ (103 mEq./L. Na^+ mixed with 3 mEq./L. K^+)†				
Control	38	0.82 ± 0.19	91.0 ± 1.20	14.4 ± 1.15
Maximum effect of perfusion	38	4.31 ± 0.19†	83.9 ± 1.18†	13.4 ± 1.08
D. After Hemorrhagic Hypotension‡				
Control	241	0.083 ± 0.014	89.68 ± 0.58	13.90 ± 0.14
After hemorrhagic hypotension	286	−1.64 ± 0.050†	94.62 ± 0.38†	14.02 ± 0.22
E. In the Marginal Zone of Ischemic Area after Coronary Occlusion‡				
Control	275	−0.188 ± 0.015	91.02 ± 0.24	13.68 ± 0.14
After coronary occlusion (25 minutes)	289	−1.53 ± 0.043†	94.07 ± 0.26†	13.63 ± 0.16
F. During Perfusion of Nonischemic Myocardium with High Na^+ (171 mEq./L. Na^+ Mixed with 3 mEq./L. K^+)‡				
Control	45	0.995 ± 0.25	91.7 ± 0.90	12.8 ± 1.17
Maximum effect of perfusion	45	−1.90 ± 0.32†	98.1 ± 0.88†	12.5 ± 1.05
G. During Perfusion of Nonischemic Myocardum with Low K^+ (0.5 mEq./L. K^+ Mixed with 142 mEq./L. Na^+)‡				
Control	36	0.79 ± 0.28	92.1 ± 0.79	13.7 ± 0.60
Maximum effect of perfusion	36	−1.61 ± 0.29†	96.3 ± 1.20†	13.6 ± 1.03

NOTE: The mean values of potential are given in millivolts, ± the standard error of the mean.

* S-T segment elevation and decrease of membrane resting potential occurred, showing a highly significant difference compared with control value.

† Highly significant difference compared with control value ($P < 0.01$).

‡ S-T segment depression and increase of membrane resting potential occurred, showing a highly significant difference compared with control value.

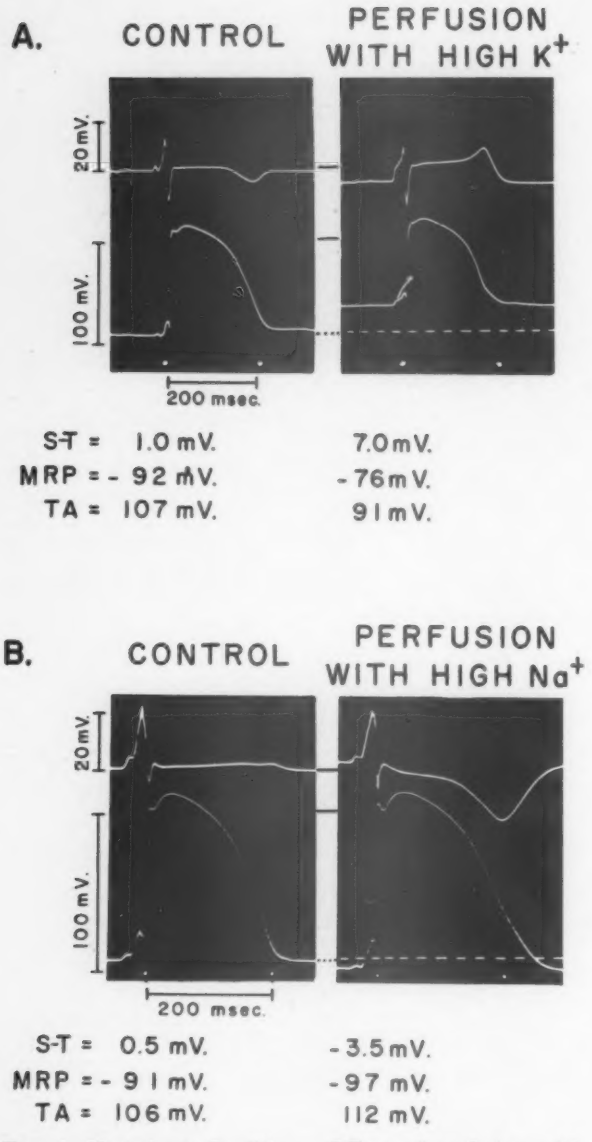


FIG. 4. *Nonischemic Conditions.* Effects of perfusion with (A) high concentration of K^+ and (B) high concentration of Na^+ on the surface and intracellular electrograms. Abbreviations as in Figure 3. A, perfusion with solution of high concentration of K^+. Note decrease in negativity of membrane resting potential, T-Q segment depression (relative S-T elevation), slight increase in R wave, decrease in S wave. B, perfusion with solution of high concentration of Na^+. Note increase in membrane resting potential, T-Q segment elevation (relative S-T depression). The intrinsic deflection (dotted line) was drawn by hand for better visualization.

least partly responsible for the S-T elevation and not just coincidental, their effect upon nonischemic myocardium was studied. For this purpose, a total of seventy-eight perfusion experiments was carried out.[19] A disturbance of transmembrane gradient was produced in dogs under nonischemic conditions by perfusing the myocardium with solutions of high K ion (forty experiments) or low Na ion concentration (thirty-eight experiments). Both solutions were close enough to normal tonicity so that hemolysis did not occur. The solution high in K^+ contained 10 mEq. per L. of K^+ mixed with a solution of normal Na^+ concentration (142 mEq. per L.). The low Na^+ solution contained 103 mEq. per L. of Na^+ mixed with a solution containing 3 mEq. per L. of K^+. The exact concentration of K^+ and Na^+ in the extracellular spaces of the myocardium during perfusion is not known. However, it is believed that the extracellular concentration of these ions became moderately higher or lower than normal as a result of perfusion. Perfusion with either of these solutions promptly resulted in the appearance of T-Q depressions and corresponding S-T elevations in the surface electrogram. These were again shown in the intracellular electrogram to be due to T-Q depressions caused by decreased negative membrane resting potential of the individual underlying cells (Fig. 4A). It is suggested that this decrease may again be due to hypopolarization of the cell membrane (Table 1B and C). In these perfusion experiments the electrolyte disturbances were of very short duration, lasting 15 to 20 seconds. Thus, while such experiments may have some similarity to subacute or chronic clinical conditions with abnormal blood electrolyte patterns, the changes in disease are obviously more complex, and cannot be expected to be identical with these experimental conditions.

Nevertheless, from the foregoing, it would seem that a *decrease in transmembrane ionic gradient* Ka^+ *and* Na^+, and undoubtedly other chemical changes, can be largely responsible for the occurrence of S-T segment elevation in severe ischemia as well as in nonischemic myocardium.

Mechanism of R and S Wave Changes: An effort was made to determine the mechanism of the development of increased amplitude of the R wave which may be seen early in severe ischemia, and also the diminution or disappearance of S waves in this condition. These phenomena were investigated by correlating surface electrograms with intracellular electrograms in normal areas and in experimentally produced areas of severe ischemia. In the normal heart it was observed that the onset of the R wave of the surface electrogram always preceded the onset of the membrane action potential of the underlying subepicardial cells. The intracellular electrogram, however, re-

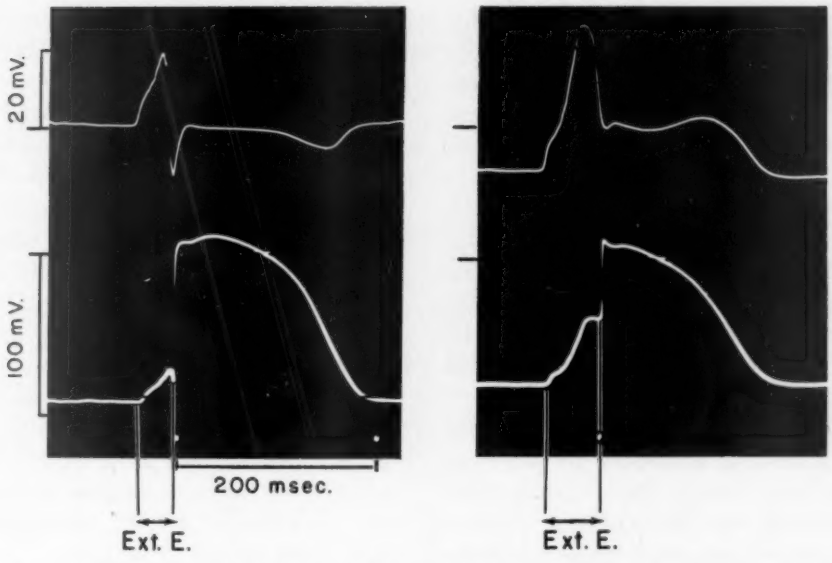


FIG. 5. Simultaneous recordings of surface and intracellular electrograms of underlying cell in control (left) and 20 minutes after coronary artery occlusion (right). Note that the onset of the R wave of surface electrogram precedes the onset of the subepicardial transmembrane action potential (MAP). Before the onset of transmembrane action potential in the intracellular electrogram, a deflection (extrinsic effect) which has similar amplitude and configuration with R wave of overlying surface electrogram is seen.

corded a delta-shaped wave corresponding to the initial portion of the surface R wave. This small delta wave is due to the action potentials of surrounding cells. It is, therefore, an extrinsic effect (Fig. 5).

In severely ischemic areas this extrinsic effect is greatly increased in amplitude and duration. As a result, the surface R wave becomes larger and wider and the S wave becomes smaller and may disappear. These findings are probably the result of delayed conduction in the ischemic muscle,[6,10,20] This localized conduction disturbance produces a situation in which the surface electrode faces potentials which are almost exclusively positive and thus records large prolonged R waves. It has been shown by Rakita et al.[26] and later confirmed[21] that when simultaneous tracings are made from intramural electrodes situated at various depths in severely ischemic myocardium, evidence of slowing of depolarization is also obtained. This conduction disturbance, as indicated by the increased amplitude and width of the R wave, was generally not apparent in the subendocardium but became progressively more severe nearer the epicardium. Because the surface R wave is so large and prolonged, the S wave is buried in it and is reduced or disappears (Fig. 5).

There also appears to be a correlation between the occurrence of large, upright T waves in acute severe ischemia and alterations in the slope of the repolarization wave of the intracellular electrogram. Tracings from individual cells show an increase in the slope of repolarization and a shortened duration of the membrane

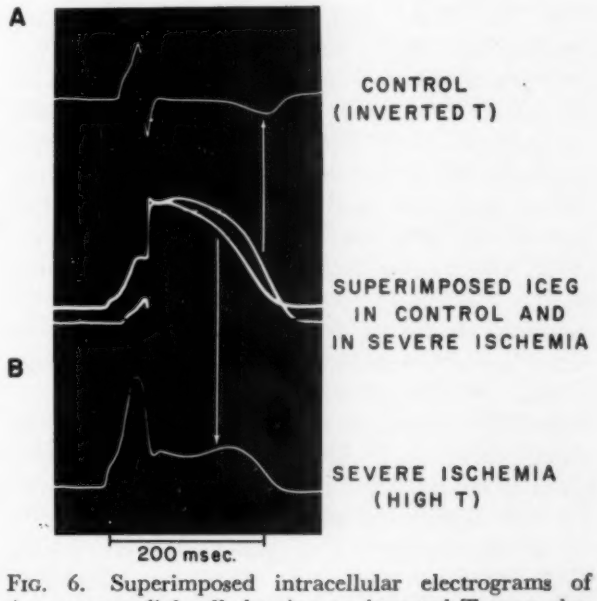


FIG. 6. Superimposed intracellular electrograms of A, a myocardial cell showing an inverted T wave due to experimental conditions and B, an acutely ischemic cell with S-T elevation. The slow repolarization phase of each tracing and simultaneous T wave configuration is shown by arrows. In acute severe ischemia the high T wave is associated with steep slope of repolarization.

action potential which may be responsible for the T wave becoming large and upright (Fig. 6). However, further studies on the fundamental causes of T wave changes in ischemia are obviously needed.

Mild Ischemia

In order to determine the fundamental bioelectrical and metabolic disturbances responsible for the electrocardiographic changes found in mild ischemia and to compare them with those found in severe ischemia, similar bioelectrical and metabolic studies were carried out.

Bioelectrical Experiments: "Islands" of mild myocardial ischemia were produced by bleeding as already described. These islands were then studied by correlating the intracellular electrogram and simultaneous overlying surface electrogram. More than 1,200 penetrations were made with the microelectrode in such areas.[22] An increase in the negativity of the membrane resting potential of these cells usually occurred. Although this was a definite and statistically significant finding, the increase in negativity of the membrane resting potential was usually not as striking as the decrease noted in severely ischemic cells.

The increased negativity membrane resting potential consistently produced a significant and proportional elevation of the T-Q level of the overlying surface of the electrogram (Fig. 3B) (Table 1D). In the clinical electrocardiogram this is manifested as relative depression of the S-T segment, as previously explained. Thus, the findings are essentially opposite to those found in severe ischemia. Since the increase in negativity of the membrane resting potential and corresponding elevation of the T-Q level are not as marked as the opposite changes in severe ischemia, it is to be expected that the clinical S-T depressions of mild ischemia would be less marked than the S-T elevations of severe ischemia. This is in general accord with clinical experience.

Similar studies were made of the relatively mildly ischemic margins of severely ischemic areas produced by coronary ligation. Moderate but significant increases in the negativity of the membrane resting potential were found, with resulting elevation of the surface T-Q segments and apparent depression of the surface S-T segments (Table 1E). These changes appear to be consistent with the findings in mildly ischemic areas produced by bleeding. They also offer an explanation of the S-T depressions sometimes observed clinically at the margins of acute severe myocardial infarctions.

It has recently been pointed out[27] that S-T depression is clinically significant of ischemia mainly when the depressed S-T segment is flat. It is possible that a partial explanation for this may be the flat configuration of the elevated T-Q segment which results from increased negativity of the membrane resting potential in mild ischemia, as shown experimentally. After the onset of ischemia the membrane resting potential assumes a new level which is maintained with little or no fluctuation. This results in a practically flat tracing for the membrane resting potential as well as the T-Q level. Hence, the S-T segment would also be expected to be flat.

Metabolic Experiments: Are the primary S-T depressions of mild ischemia associated with chemical disturbances, as was found with the S-T elevations of severe ischemia? In order to investigate this possibility the K and Na ion concentrations of arterial and venous blood were studied in mildly ischemic myocardium in which S-T depressions were recorded.[15] The K ion concentration of the venous blood was generally less than that of the arterial blood and the Na ion concentration generally higher. Therefore, intracellular potassium concentration must have become higher than normal limits and intracellular Na^+ concentration probably diminished. Thus, in these areas the transmembrane ionic gradients of K^+ and Na^+ were significantly higher than in areas where the S-T segment was isoelectric.

The increased uptake of K^+ by the mildly ischemic cells may be explained theoretically as follows: In normal cells energy is supplied chiefly by aerobic breakdown of glycogen. In mild ischemia, however, the energy demands of the cells are supplied largely by anaerobic breakdown of glycogen because of the limited oxygen supply. The anaerobic catabolism of glycogen calls for an increase in cellular uptake of glucose. Since glucose has an affinity for K^+, it carries K^+ with it into the cell.[23,24] Thus, the transmembrane ionic concentration gradient of K^+ increases. This may well result in a state of hyperpolarization by increasing the electrical charges on the membranes of the mildly ischemic cells.

In order to determine whether chemical changes alone, without ischemia, could be responsible for primary S-T depression, per-

CHART I

Theoretical Chain of Events in Ischemia and Nonischemic Conditions with Electrolyte Alterations

(1) Severe Acute Ischemia	(2) Electrolyte Alterations in Nonischemic Conditions	(3) Mild Ischemia
Cell Membrane Injury (partially loses ability to maintain ionic concentration gradient)		Increased Metabolism of Glucose and Potassium
↓		↓
Decreased Transmembrane Ionic Concentration Gradient for K^+ and Na^+	← High K^+ Low Na^+ (extracellular fluid) → High Na^+ Low K^+	Increased Transmembrane Ionic Concentration Gradient for K^+ and Na^+
↓		↓
Decreased Membrane Resting Potential (hypopolarization)		Increased Membrane Resting Potential (hyperpolarization)
↓		↓
T-Q Depression Relative S-T Elevation		T-Q Elevation Relative S-T Depression
.....		.....
Increased Amplitude of R Wave (sometimes "giant" R wave), Decrease or Disappearance of S Wave, Amplitude of T Wave Usually Increased.		Sometimes Decreased R Wave, Increased S Wave

CHART I. Theoretical interrelations of metabolic and bioelectrical events based on the experimental data during ischemic and some nonischemic conditions. Column 1 shows what may theoretically occur as a result of *severe* ischemia. Column 3 shows the theoretical sequence of events after *mild* ischemia. Column 2 shows the theoretical sequence of events in nonischemic conditions but in the presence of the identical electrolyte dusturbances.

fusion of normal myocardium was carried out in eighty-one experiments with solutions of low K^+ concentration (thirty-six experiments) or high Na^+ concentration (forty-five experiments).[19] Both procedures promptly and consistently resulted in T-Q elevation (relative S-T depression). The membrane resting potential in the intracellular electrogram increased simultaneously (Fig. 4B). It is suggested that the increase in membrane resting potential can be explained in terms of hyperpolarization of the cell membrane (Table 1F and G). Hence, it seems that *an increase in the gradient for K and Na ions*, and probably other chemical factors, are responsible for the increased membrane resting potential and primary S-T depressions seen in mild ischemia.

COMMENTS

Those who wish to view these metabolic and bioelectrical changes in mildly ischemic cells as a homeostatic mechanism might argue that such cells, by accumulating excess K^+ and glucose, are better prepared than normal cells to withstand an increase in ischemia which tends to damage the cells severely and causes a loss of K^+ from them. Having stored K^+ (and glucose) during mild ischemia, a subsequent loss of K^+ due to severe ischemia might be tolerated better than if the cell had not accumulated such an extra reserve. If these metabolic phenomena displayed by mildly ischemic cells are a protective device, it would offer an explanation for the observation that their bioelectric and electrocardiographic manifestations are almost opposite from those of severely ischemic cells.

The theoretical chain of events in severe and mild ischemic conditions and in nonischemic conditions produced by electrolyte alterations may be postulated as shown (Chart 1).

In severe ischemia there is injury of the cell and its membrane. The membrane loses some of its ability to maintain a normal ionic concentration gradient. The decreased gradient occurs because excessive amounts of K^+ leave the cell and excessive amounts of Na^+ enter the cell from the extracellular fluid. This is followed by a decrease in negativity of the membrane resting potential—hypopolarization. The decrease in membrane resting potential results in apparent S-T elevation in the clinical electrocardiogram. Associated with this are "giant" R waves and small S waves due to slowing of the

depolarization wave. If the extracellular fluid becomes abnormally high in K ion concentration or low in Na ion, even in the absence of ischemia, the transmembrane ionic gradient will be decreased for these ions and the same train of electrical events may occur.

In conditions of mild ischemia, glucose and potassium uptake of the cell is increased. The transmembrane ionic gradients for potassium and probably sodium are increased. This causes increased negativity of the membrane resting potential or hyperpolarization. The result is S-T depression. Associated with this, decreased R waves and increased S waves are occasionally seen. In the absence of ischemia, low K ion concentration or high Na ion concentration in the extracellular fluid will also increase the transmembrane ionic concentration gradient and the same electrocardiographic changes may result as in mild ischemia.

Because of the electrographic findings in the nonischemic myocardium, resulting from electrolyte changes alone, the literature on this subject was examined. At least forty different clinical conditions were found in which S-T segment deviation may sometimes occur without myocardial ischemia.[25] These conditions are often associated with marked chemical disturbances in the systemic blood serum. Thus, it is suggested that these S-T deviations may be also related, at least in part, to changes in the transmembrane ionic concentration gradient in the myocardial cells. From a practical point of view it is, therefore, important always to consider chemical changes in the systemic blood as a possible cause of electrocardiographic changes. S-T depression similar to those found in classic angina pectoris may be seen, for example, in children with marked K^+ depletion resulting from severe intractable diarrhea.

The foregoing experimental and clinical observations appear to offer a reasonable but undoubtedly incomplete explanation for the electrocardiographic findings in mild and severe myocardial ischemia and in some nonischemic conditions.

Summary

Severe ischemia results in serious damage to myocardial cells and their membranes. As a consequence, K^+ is lost from these cells and intracellular Na^+ concentration probably rises. These changes produce a decrease in the transmembrane ionic gradient for these substances and probably hypopolarization of the cell membranes. This is manifested in the intracellular electrogram by a decrease in negativity of the membrane resting potential of the individual subepicardial ischemic cells. In direct electrograms from the epicardium over these cells the T-Q segment becomes depressed. This T-Q depression is indicated in the clinical electrocardiogram as S-T elevation.

Perfusion of nonischemic myocardium with solutions of high K^+ or low Na^+ concentration produces intracellular and surface electrographic changes similar to those of severe ischemia. This supports the theory that metabolic changes such as those just described are at least part of the fundamental cause of the electrocardiographic changes of severe ischemia. In all probability, other chemical and metabolic factors also play a role in their production.

Mild ischemia produces an increased uptake of K^+ and probably glucose by the myocardial cells. As a result, the transmembrane ionic gradient for K^+ increases and a state of hyperpolarization may occur. This causes an increase in membrane resting potential of the individual cells, manifested in the overlying surface electrogram by elevation of the T-Q segment. In the clinical electrocardiogram this appears as S-T depression.

Perfusion of nonischemic myocardium with solutions of low K^+ or high Na^+ ion concentration produces intracellular and surface electrocardiographic changes similar to those of mild ischemia. This again provides support for the belief that such metabolic changes may be in part responsible for the electrocardiographic phenomena of mild ischemia.

The increase in amplitude of the R wave often observed early in severe ischemia appears to be the result of delayed conduction in the ischemic muscle. The tall R wave is also widened because of this delay. The S wave is buried in the wide R wave and thus becomes smaller or entirely invisible.

The increase in intracellular K^+ and glucose in mild ischemia may represent a homeostatic mechanism by which the cells prepare themselves for injury by severe ischemia. The fact that the electrographic and electrocardiographic phenomena of the two kinds of ischemia are almost opposite in nature then becomes understandable as a manifestation of such a mechanism.

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Report on Therapy

Digitalization by Combined Intravenous and Oral Administration of Two Glycosides*

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ONE OF THE common problems of digitalization in acutely ill patients is represented by the fact that the physician often prefers to treat such patients by a rapidly acting, intravenously administered digitalis glycoside. Following the initial effect, it is necessary to continue digitalization with a more slowly eliminated oral preparation. However, the rapidly acting glycoside (digoxin or deslanoside C) is also rapidly eliminated. Therefore, it is difficult to decide on a plan of digitalization with a slower glycoside (digitoxin) because of the interaction of two preparations with different rates of accumulation and dissipation.

Knowing that the average rate of dissipation of deslanoside C is about 20 per cent a day and of digitoxin about 7 per cent a day,[1] a theoretic scheme can be devised. However, only a practical, empirical study can supply the final answer by showing which dosage is followed by the minimal number of patients who were either incompletely digitalized or presented the toxic phenomena of overdigitalization.

Similar studies were made by Hellman and Porter[2] and Crouch.[3] However, since they used oral acetyldigitoxin after intravenous deslanoside, their findings cannot be exactly compared with those of the present study.

METHOD

A total of 102 patients were digitalized. The patients were in congestive heart failure and had not received any digitalis glycoside for at least three weeks prior to the onset of treatment.

The patients ranged in age from forty-nine to ninety-five years (average seventy years), and the cardiac diagnosis included both right- and left-sided cardiac decompensation as a result of coronary, hypertensive, or rheumatic heart disease, or chronic or acute cor pulmonale.

The criteria for decompensation (whether right- or left-sided) included the clinical observation of dyspnea, orthopnea, tachycardia, weight gain, pedal edema, ascites, pulmonary râles or pleural effusion, distended neck veins, hepatomegaly with tenderness and positive hepatojugular reflux, cardiac enlargement (detected both on percussion and by roentgenology), the presence of gallop rhythm on auscultation, and the finding of elevated venous pressure and prolonged circulation times. Not all the patients of this study presented each of the aforementioned symptoms and signs. However, these objective findings were looked for and used to evaluate the progress and efficacy of digitalization.

Underdigitalization was admitted when these clinical data disappeared slowly or recurred. *Overdigitalization* was considered present if the patient complained of visual disturbances, vertigo, nausea or vomiting, or if bigeminy, grade 1 A-V block or severe tachycardia were found. Death occurred in two cases of the entire series. The possible connection between this occurrence and excess of digitalization was taken into consideration but not conclusively proved.†

Methods of Digitalization: Table 1 illustrates the five schemes of digitalization which were followed. All five schemes employed the use of a standard and equal dose of an intravenous digitalis preparation (Cedilanid®-D) for the rapid initiation of digitalization. The schemes differ thereafter only in the dosage and time of initiation of oral digitoxin (Crystodigin®).

† Death occurred several days after the intravenous injection of digitalis glycoside. Therefore, no direct connection between injection and death was admitted. The possibility of overdigitalization by mouth as a cause of death is even less likely.

* From the Department of Medicine of the Chicago Medical School; the Division of Cardiology of the Chicago Medical School and Mount Sinai Hospital; the Parkview Rose Eisenberg Memorial Home; and the Orthodox Jewish Home for the Aged, Chicago, Illinois.

TABLE I
Schemes of Digitalization

Group No.	Scheme	
Group 1	Initial dose of Cedilanid—4 cc. =	0.8 mg. intravenously
	Digitoxin—on same day	0.8 mg. within 2 hr.
	Digitoxin—second day	0.4 mg.
	Digitoxin—third day	0.2 mg.
	Maintenance dose of digitoxin	0.1 mg.
Group 2	Initial dose of Cedilanid—4 cc. =	0.8 mg. intravenously
	Digitoxin—on same day	None
	Digitoxin—second day	0.8 mg.
	Digitoxin—third day	0.4 mg.
	Digitoxin—fourth day	0.2 mg.
	Maintenance dose of digitoxin	0.1 mg.
Group 3	Initial dose of Cedilanid—4 cc. =	0.8 mg. intravenously
	Digitoxin—on same day	0.4 mg. within 2 hr.
	Digitoxin—second day	0.4 mg.
	Digitoxin—third day	0.2 mg.
	Maintenance dose of digitoxin	0.1 mg.
Group 4	Initial dose of Cedilanid—4 cc. =	0.8 intravenously
	Digitoxin—on same day	0.2 mg. within 2 hr.
	Digitoxin—second day	0.2 mg.
	Digitoxin—third day	0.2 mg.
	Maintenance dose of digitoxin	0.1 mg.
Group 5	Initial dose of Cedilanid—4 cc. =	0.8 mg. intravenously
	Cedilanid—6 hr. after injection	3 mg. orally
	Cedilanid—second day	1 mg. orally
	Cedilanid—third day	1 mg. orally
	Maintenance dose of Cedilanid	0.5 mg. orally

Scheme five substitutes oral Cedilanid-D in tablet form for the digitoxin used in the other groups.

The majority of the patients were hospitalized, thereby facilitating a constant monitoring of their progress as well as an objective evaluation of their response to digitalis. All patients, whether hospitalized or seen on a regular outpatient basis, were followed up for a minimum of three weeks and a maximum of four months, before inclusion in the study.

During the course of digitalization, the patients were given no standard diuretic agents, either parenteral or oral, and no antihypertensive medication but were on a low sodium diet.

In our study, each of the five groups represented what we considered to be a typical cross section of the gradient of cardiac failure, ranging from mild to most severe. During the course of this project, we eliminated a small group of patients with severe congestive failure and pulmonary edema, secondary to myocardial infarction or cerebrovascular accident. This group was given repeated intravenous injections of Cedilanid-D following the initial dose of Cedilanid-D. However, because of the severity of the underlying disease (i.e., myocardial infarct or cerebrovascular accident), many of these patients died before an adequate analysis of the efficacy of digitalization could be made.

RESULTS

Table II demonstrates the results of the five schemes of digitalization.

Group 1 (twenty-six cases) had one case with fatal outcome and four cases with toxic effects, while only one patient seemed inadequately digitalized. It was concluded that the oral dose of digitoxin (0.8 mg. soon after the initial injection) was excessive. The same was admitted for group 2 (twenty-one cases) in which there was one fatality and three cases with toxic effects: the dose of digitoxin (0.8 mg. on the second day) was still too high. Again, group 5 showed toxic effects in three of twelve cases: the dose of oral Cedilanid-D was apparently too high.

Good results were found in general in group 4 (22 cases) but, while one patient still had toxic effects, two patients were definitely underdigitalized. The dose of oral digitoxin (0.2 mg. every day, starting on day of injection) was probably too low for the average patient.

Group 3 gave the best results in our study. The scheme consisted of an intravenous injection

TABLE II
Results of Various Schemes of Digitalization

Group No.	No. of Cases	Good Results	Toxic Effects	Inadequate Digitalization	Fatal Outcome	Conditions
Group 1	26	20	4	1	1	Excessive dosage
Group 2	21	17	3	0	1	Excessive dosage
Group 3	21	20	0	1	0	Optimal dose
Group 4	22	19	1	2	0	Near optimal dose
Group 5	12	8	3	1	0	Excessive dosage
Total cases	102	84	11	5	2	

of 0.8 mg. Cedilanid-D, followed by the oral administration of 0.4 mg. digitoxin on the same and the following day, 0.2 mg. on the third day, and a maintenance dose of 0.1 mg. starting on the fourth day. None of the twenty-one patients had toxic effects, no fatality occurred, and only one was underdigitalized. Physiologically and pharmacologically this can be readily understood by considering the ratios of dissipation of deslanoside and digitoxin, and the probable resulting rate of accumulation (Fig. 1). The curve resulting from the addition of digitoxin to deslanoside by weight gives an initial peak followed by a stable line. However, if one considers that the average digitalizing dose of deslanoside is 1.6 mg. and of digitoxin is 1.2 mg. (DeGraff[4]), the curve of the total percentage of the digitalizing dose obtained reaches the optimum on the second day and then follows a stable line near 100 per cent (Fig. 1).

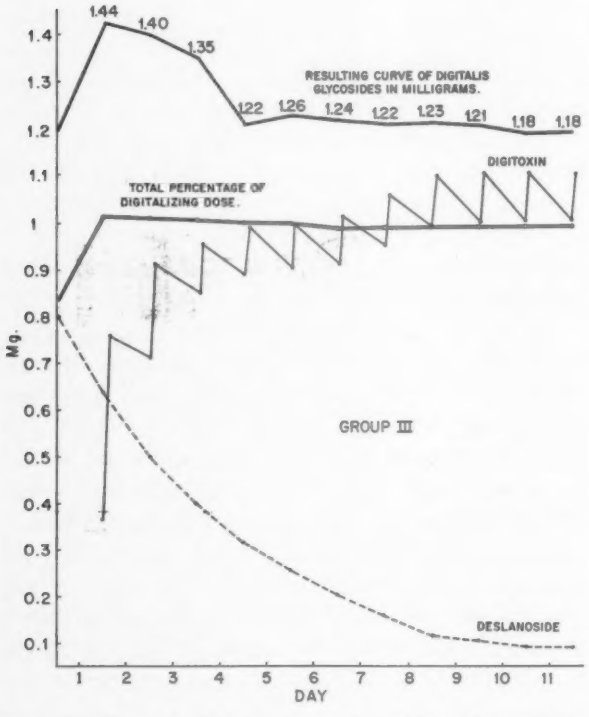


FIG. 1. Doses of digitoxin and deslanoside used in group 3. Curves of deslanoside and digitoxin were made on the basis of their daily dose of administration and their accepted rate of elimination. Resulting curve obtained by simple addition of milligrams of both glycosides. Total percentage of the digitalizing dose obtained by adding the percentage of the digitalizing dose of each glycoside. While the curve by weight shows an initial peak, the total percentage of digitalizing dose shows a remarkable stability throughout.

COMMENTS

Even though no cases of heart failure are exactly comparable, the patients in our study were similar in regard to age and severity of heart failure. By comparing groups 1 to 5, the conclusion seems to be that, after initial intravenous digitalization with Cedilanid-D, the best scheme is to give 0.4 mg. digitoxin on the same day, between 0.2 and 0.4 mg. on the following two days, and then put the patient on a maintenance dose of 0.1 mg. A slightly less effective scheme consisted of 0.2 mg. of digitoxin on the day of the intravenous injection, followed by 0.2 mg. on the second and third day, and then by the maintenance dose.

SUMMARY

A group of 102 patients was studied in an attempt to arrive at a scheme of digitalization employing intravenous Cedilanid-D at first, and then oral digitoxin. Various schemes were followed to see which produced the best therapeutic effects and the smallest incidence of either toxicity or inadequate digitalization.

The scheme found most effective consisted of intravenous Cedilanid-D 0.8 mg. followed by oral digitoxin 0.4 mg. on the same day and the following day, then 0.2 mg. on the third day followed by a daily maintenance dose of 0.1 mg. digitoxin. A slightly less effective scheme consisted of 0.2 mg. on the day of the intravenous

injection followed by 0.2 mg. on the second and third day, and then by the maintenance dose. As the other schemes were less satisfactory, it was considered likely that the optimal dose in the individual case may vary between that used in the two schemes just mentioned. The higher dosage should be employed in the more severe cases of failure while the other may be reserved for the milder forms.

ACKNOWLEDGMENT

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Historical Milestones

John Eberle's Lectures on Medicine (1827)

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JOHN Eberle (1788–1838), a well known medical editor, author, practitioner and teacher, was one of the founders of the Jefferson Medical College. He taught materia medica and the theory and practice of medicine at that institution in its earliest days. Later he became involved in the tempestuous vicissitudes of the Medical College of Ohio and the rival school at Louisville. Both in Philadelphia and in Cincinnati he was for various periods a colleague of the ubiquitous Daniel Drake.

Eberle's most important writings are his *Treatise of the Materia Medica and Therapeutics* (two volumes, 1822 to 1823) which enjoyed high esteem for some years, and his *Treatise on the Practice of Medicine* (1830). The latter work was the more popular but in the opinion of Thomas D. Mitchell, Eberle's colleague and biographer, was a less important contribution.*

In addition to his major writings Eberle published a compendium titled *Notes of Lectures on the Theory and Practice of Medicine, Delivered in the Jefferson Medical College*, 252 pages, Philadelphia, 1827, Auner. This book, like most others of its kind, makes no pretense of literary grace. Instead it is filled with abrupt, concise sentences which convey the principal content of the lecturer's offering. Consequently the modern reader is given, as it were, a biopsy, which reveals in small compass what was taught to students at one American medical college in the third decade of the nineteenth century.

* * *

EXCERPTS FROM EBERLE'S "NOTES"

PREFACE

This little work is published expressly for the use of the students attending the author's lectures on the Theory and Practice of Medicine. It embraces little more than the main propositions and facts, which form the ground-work of the lectures; in other words, the *text* upon which he enlarges and comments in extemporary discourse; and which, especially, the student ought to impress upon his memory. The practice of taking notes, though attended with some advantages, is nevertheless, on the whole, calculated to lessen the benefits to be derived from oral instruction. The train of thought and reasoning is interrupted; and the mind irregularly hurried along the current of the speaker's observations—seizing sometimes upon remarks that are comparatively unimportant, at the expense of others of a more useful and interesting import; and losing in a great measure the general spirit and scope of the speaker's discourse, more especially when the subject is one of general disquisition. These disadvantages, it is believed, will be diminished, if not wholly obviated, by works constructed on the plan of the present one. Being secure of the *text*, or propositions, the student may yield his mind, without embarrassment, to the explications and discussions of the lecturer. His efforts, too, in recalling to his mind the observations he may have heard from the speaker, will be greatly favoured, by looking over, in private, the sketch which is thus placed in his hands.

The author acknowledges, that this manual does not come up to the idea he has formed, of the proper construction of a *text-book* of this kind; but, such as it is, he flatters himself, that it will in some degree answer the intentions for which it was composed; and with this hope, he respectfully dedicates it to those students of

* MITCHELL, T. D. John Eberle. In: Gross, S. D. Lives of Eminent American Physicians and Surgeons, pp. 460–478. Philadelphia, 1861. Lindsay and Blakiston.

medicine, who do him the honour of attending his lectures. . .

ANGINA PECTORIS

Symptoms: Sudden and violent pain about the sternum, extending to the arms, attended with great anxiety, difficulty of breathing, and a sense of suffocation; pulse seldom materially affected—sometimes irregular or intermitting; countenance pale, and expressive of intense anxiety; extremities cold. The attack usually comes on while the patient is walking. At first, it lasts but a few minutes, and returns after long intervals; but by degrees the fits recur oftener, and become more protracted.

Predisposition: It occurs more frequently in males than females; and exceedingly seldom in young persons. Subjects of a gouty or rheumatic habit, with a tendency to corpulency, are most liable to the disease.

Causes: Ossification of the *coronary arteries*, and *valves* of the heart; dilatation of its ventricles; a *softened structure* of the heart, and other organic affections of this organ, and of the adjoining parts. In some cases, however, not the slightest traces of structural derangement are found on dissection. Dr. Johnson thinks that a neuralgic affection of the *cardiac plexus* may produce it—an opinion which is, I think, well founded. From all that has been ascertained in relation to this subject, it would seem, that angina pectoris is an affection which may be excited by a *variety* of causes; and it appears to me probable, that the essential nature of the disease, consists in an *irritated condition of the cardiac nerves.*

Prognosis: The disease is generally believed to be incurable; and when it depends on structural derangement of the heart, it undoubtedly is so. There are some well attested cases on record, however, which yielded to remediate measures. Death almost always occurs suddenly. Fothergill, Wichmann.

Treatment: For the relief of the paroxysm, bleeding, opium, hyoscyamus, a recumbent posture, and perfect rest and quietness, are often found beneficial. To prevent the return of the disease, the following remedies have been employed with advantage. Guaiacum; opium, musk, and camphor, in union, (Shaeffer); cicuta, assafoetida, and camphor, (Johstone); flowers of zinc and opium, (Perkins); lime water and antimony, (Smith); frictions with tartar emetic ointment on the breast, (Godwin); phosphoric acid, (Baumes, Richter); James's powder, (Smith); a rigid antiphlogistic regimen, (Odier); arsenic, (Hufeland, Blane); prussic acid; hyoscyamus; stramonium; cuprum ammoniacum, &c. All kinds of spirituous drinks are injurious; so are strong mental emotions; inordinate venereal indulgence; strong corporeal exertions; sudden atmospheric vicissitudes; indigestible and irritating articles of food, &c.

DROPSY

Pathology of Dropsy: Dropsical effusion is not, properly speaking, a disease, but only an effect of disease. The morbid condition upon which dropsical effusions depend, is either inflammation, or a state of the exhalants closely allied to inflammation. (Rush.) The doctrines which allege, that torpor of the absorbents, or relaxation of the exhalants, is the proximate cause of the effusion, are examined, and their insufficiency pointed out. There is, no doubt, always deficient venous absorption, because that condition of the capillaries, which disposes to excessive exhalation, is essentially connected with a congested state of these vessels, and congestion, or vascular fulness, always impedes absorption. (Magendie.) Observations on the character of the urine in hydropic diseases. In some instances, the urine contains more or less serum; in others, it is entirely destitute of it. According to the observations of Blackall, Willis, and Ayre, it is in the sub-acute and idiopathic forms of dropsy, that the urine is loaded with the greatest quantity of serum. In dropsy from scarlatina, there is generally a large quantity of serum in the urine. In local dropsies, not attended with general excitement, the urine is seldom charged with any serum. (Ayre.)

When the heart sympathizes with the local or general morbid action of the exhalants, febrile symptoms attend. When the morbid excitement of the exhalants does not extend to the heart, the general circulation is languid, and debility and relaxation characterize the disease.

The general indications in the treatment of dropsy, are: 1. To procure the absorption and elimination of the effused fluid; 2. To correct the morbid action of the serous exhalants, from which the effusion takes place.

Dropsy is divided into three principal varieties: viz. *Anasarca*, *ascites*, and *hydrothorax*.

ANASARCA

In this variety, the effusion takes place into

the cellular tissue. It may be either local or general. A part that is anasarcous, pits, on pressure. It almost always begins in the feet or legs—the swelling diminishing during the night, and increasing towards evening. The urine in this, as in the other varieties of dropsy, is always scanty and high coloured; the countenance is sallow, the general system sluggish, and there is usually much sleepiness. Anasarca is frequently connected with effusion into the abdomen and chest.

Causes: Local anasarca may be produced, by whatever impedes the return of the blood from a part, as, indurated glands pressing on large veins, ligatures, &c. It arises also from mere general debility; diseases of the heart; phthisis, &c.

General anasarca may result from hemorrhages, diarrhoea, diabetes, and other circumstances that rapidly exhaust the system. Observations of the manner in which these causes produce dropsy. *Sudden suppression of perspiration*, particularly after scarlatina, measles, or while under the influence of mercury, a frequent cause of general anasarca. Dropsy from this cause always decidedly phlogistic. General anasarca may also result from the internal use of arsenic—from torpor of the kidneys—from amenorrhoea, general plethora, with a relaxed habit, chronic diseases, *intestinal irritation*, &c. Observations on the modus operandi of these causes.

Proximate cause: A sub-inflammatory action of the exhalants of the cellular tissue, attended with increased exhalation, and diminished venous absorption. It appears to be probable, that congestion in the *venous* capillaries, performs an important part in the production of dropsical accumulations. This idea is discussed, at length, in the lecture.

ASCITES

Abdominal Dropsy: Its causes are sometimes *local*, at others *general*. The local causes are such as impede the circulation through the portal system of vessels among which, visceral indurations, particularly of the liver and spleen, are the most common. Dr. Ayre denies that visceral obstructions produce dropsy; they notwithstanding frequently do so. The most common general cause of ascites, is *cold*, either generally or locally applied. When the result of this cause, its character is always conspicuously inflammatory; the blood usually exhibiting the buffy coat; the skin being dry and hot; the pulse frequent and tense, and the urine loaded with serum. Ascites is seldom wholly free from anasarca. Intestinal irritation, sometimes gives rise to abdominal dropsy. It occurs as the sequel of peritonitis. *Diagnosis.*

Proximate cause: A morbid action of the exhalants of the peritoneum, attended with capillary congestion, and diminished absorption.

HYDROTHORAX

Serum effused into the cavity of the thorax. It is characterized by the following:

Symptoms: Oppression in the chest; difficult respiration, particularly when lying down, or ascending heights; dry cough; a sense of suffocation, when in a recumbent position; sudden starting during sleep; pulse intermitting, or irregular; thirst considerable; urine scanty; oedema of the feet; a pale bloated countenance, &c. Divided into *symptomatic* and *idiopathic*. The first arises from *organic affections*, the latter from *general causes*.

Causes: Organic affections of the heart. When from this cause, the effusion occurs on both sides. *Chronic pleuritis*, a frequent cause of hydrothórax. It may also result from a tuberculous state of the pleura, and even from structural disease of the stomach and liver. This is by far the most frequent variety of hydrothorax, and is almost always incurable.

Idiopathic hydrothorax, is of very rare occurrence, and generally easily cured. The effusion almost always occurs only on *one* side, that side becoming sometimes considerably enlarged, by the pressure of the fluid.

General plethora, predisposes to hydrothorax; particularly in persons who have passed the middle period of life, and who indulge in the pleasures of the table, and use but little exercise.

Diagnosis: A sense of suffocation on lying down, and on firm pressure on the abdomen, will generally distinguish it from mere organic disease of the heart. Percussion, produces a *dull* sound, and the *stethoscope* detects the absence of the respiratory murmur.

Treatment: When the heart sympathizes with the primary local irritation, or with the morbid action of the capillaries from which the effusion occurs, *blood-letting* is an important remedy. It is indicated in all cases, in which there is tension and quickness of the pulse. *Local* bleeding, from the thorax or abdomen, recommended by Ayre, in hydrothorax and ascites.

Diuretics are important remedies in hydropic diseases. Their operation is, however, rather

palliative than curative, that is, they evacuate the effused fluid, rather than correct the morbid action on which the effusion depends. In full and phlogistic habits, their operation is promoted by bleeding and cathartics. When the effusion is very extensive and the blood has been deprived of a great portion of its serum, copious draughts of water promote the operation of diuretics. The mode in which diuresis removes dropsical effusions, explained. The most useful diuretics in dropsy, are: squills, digitalis, tobacco, cantharides; acetate, nitrate and tartrate of potash; colchicum, wild carrot seed, erigeron heterophyllum and juniper berries.

The *squill* is the best diuretic in hydrothorax. It is best adapted to cases in which the urine is very scanty, high coloured, and sedimentous, and not attended with much febrile excitment. Its virtues are much enhanced, by giving it in union with calomel, especially in hydrothorax. Very advantageously combined with digitalis and nitre. The reason why calomel and squills, in combination, are more beneficial in hydrothorax, than in the other varieties of dropsy, are three-fold; "1. absorption; 2. diuresis; 3. determination to the glands of the mouth and throat, causing a derivation from the vessels of the pleura."

Digitalis: Some greatly extol its virtues in dropsy, others speak lightly of it. It does not appear to do much good, in subjects of a *tense* fibre, and robust habits of body. In persons of a contrary habit, with a pale countenance, cold skin, and weak pulse, it often proves decidedly beneficial. (Withering, Maclean.) *Digitalis* is the best diuretic in dropsies following scarlatina. It is almost always beneficial, when the urine is coagulable by heat, small in quantity, somewhat turbid, and depositing a branny sediment, when cold. (Blackall.) It almost always fails to do good, when the urine, though serous, is pale, crude, and without sediment. It is generally given, in combination with squill or calomel. I prefer giving it in union with nitre and calomel. In feeble habits it may be advantageously combined with opium.

Cantharides, more particularly useful in anasarca, after scarlatina. (Ferriar.) Nitre is an excellent remedy, when the febrile excitement runs high. Diuretic drinks, such as infusion of juniper berries, wild carrot seed, &c. should be freeely allowed.

Cathartics: Valuable remedies in ascites and anasarca—not so in hydrothorax. Their modus operandi explained. The articles of this class, most beneficial, are: tartrate of potash; elaterium; gamboge, &c. Of these, the tartrate of potash is both the safest and the most useful. I have employed the following cartharo-diuretic composition, with more uniform and prompt advantage, than any other article, or combination of articles, I have ever tried. R. Tart. potas. ℥iss. Sulph. potas. ℥ss. Pulv. Scillae, ℥ij. Tart. Antimonii, gr. ij. Dose, a teaspoonful, four or five times daily. This rarely fails to excite very copious watery stools, and at the same time, free diuresis. It is particularly useful in ascites. I have generally derived much more benefit from gamboge, than from elaterium. It may be advantageously combined with cream of tartar, in the proportion of 2 grains of the gamboge, to 30 to the latter article, repeated every three or four hours. It produces copious watery stools.

Mercury is a remedy of valuable powers in hydropic diseases. Generally given in union with diuretics, particularly squills and digitalis. Should be given until the mouth is slightly affected by it. Relaxed and scorbutic habits, inimical to its beneficial influence. Especially valuable, where there is organic disease of the liver.

Sulphuret of Iron: I have seen much good done by this article, in cases attended with a relaxed and very debilitated state of the system; particularly in the anasarca of females, from excessive sanguineous discharges. It acts as a powerful diaphoretic, as well as tonic.

Diaphoretics, are indicated, when the disease is the consequence of suppressed perspiration from cold. Antimonials, in such cases, act beneficially.

Blisters, and rubifacients, to the chest or abdomen, in hydrothorax and ascites are strongly recommended by Ayre. I have seen much good derived from a blister over the abdomen, in a case of ascites. *Tapping*. . .

* * *

AUTHOR'S COMMENT ON EBERLE'S "NOTES"

As Eberle's preface indicates, the book is an outline of his lectures. It was published in order to obviate note-taking, to which Eberle objected because it distracted the students' attention from the discourse.

The description of angina pectoris is laudably clear and accurate. Eberle recognized that a variety of lesions, or none, might be found at autopsy. For this reason he subscribed to the common opinion that the basic cause was

irritation of the cardiac nerves. For treatment of the paroxysm he advocated bleeding, opium, hyoscyamus and rest in bed. On the score of prevention he mentions a bewildering list of drugs which had been recommended by various authorities. Contrary to the correct teaching of Heberden, Eberle states that all kinds of spirituous drinks are injurious.

Eberle used the word dropsy as a general term to include anasarca, ascites and hydrothorax. He recognized that dropsy is not an independent disease. At the same time he confused inflammatory and noninflammatory edema. He knew that in postscarlatinal dropsy the urine contains albumen ("serum").

He recognized that local swelling might be produced by local impediment to venous flow as well as by diseases of the heart. General anasarca might result from various disturbances including hemorrhage, diarrhea and, interestingly enough, diabetes. An additional cause is the sudden suppression of perspiration; this belief perhaps is a survival of ancient humoralism.

The section on hydrothorax is especially interesting to both the clinician and the medical historian. Eberle states succinctly that in hydrothorax percussion produces a dull sound and the stethoscope detects the absence of the respiratory murmur. In other words, percussion and auscultation were regularly mentioned in the lectures given to students at Jefferson as early as 1827, only eight years after Laennec's first edition.

The treatment of hydrothorax as described by Eberle consisted of bloodletting and the use of diuretics. The latter include squills, digitalis, tobacco, cantharides, potassium salts and other drugs. Of these medicines Eberle considered squills the best. It might be given in combination with calomel, digitalis or potassium. He considered digitalis to be of uncertain reliability but most useful in postscarlatinal dropsy, when the urine was scanty and was coagulable by heat. Cathartics were believed to be more valuable in ascites and anasarca than in hydrothorax.

Case Reports

Idiopathic Enlargement of the Right Atrium*

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DESPITE THE increased incidence of recognition of unusual forms of heart disease, there remain many cases in which the etiology is obscure. Among these is "idiopathic" cardiac enlargement, usually involving the left ventricle, the whole heart[1-3] or, sometimes, the right side of the heart.[4] Three patients with massive enlargement of the right atrium but without significant enlargement of the rest of the heart have been observed. The etiology of the enlargement is not known and this may be an unusual congenital malformation.

CASE REPORTS

CASE 1. A 25 year old man, who had been asymptomatic and in apparently excellent health, was admitted to the Philadelphia Veterans Administration Hospital on December 8, 1955 because of an abnormal cardiac silhouette discovered on a routine pre-employment roentgenogram of the chest. Review of the army induction films of this subject taken in October 1941 showed the same cardiac configuration.

Physical examination revealed no significant abnormality. All routine laboratory studies were within normal limits. Electrocardiograms revealed slight flattening of some of the T waves and frequent atrial premature beats with aberrant ventricular conduction (Fig. 1A).

Roentgenologic examination disclosed an unusual cardiac silhouette with enlargement to the right (Fig. 2). The possibility that this represented a cardiac chamber was considered, but careful examination of the films convinced most observers that the abnormal contour was more likely due to a pericardial cyst or a tumor mass adjacent to the heart. On fluoroscopic examination the lesion did not appear to pulsate. In a planigram it could not definitely be separated from the heart, but its lobular appearance and encroachment on the right lower lobe bronchus were thought to suggest neoplasm (Fig. 3). A small rounded density was present in the right midlung field.

Angiocardiography was not performed because the conventional studies seemed to indicate that the abnormal bulge was not a cardiac chamber. Exploratory thoracotomy without further delay was recommended because of the possibility of neoplasm.

Operative Findings: At operation a markedly enlarged and dilated right atrium and right atrial appendage were found. The right ventricle was thought to be slightly enlarged but the other chambers were not remarkable. There were no thrills over the heart or the great vessels. The distribution of the pulmonary veins, venae cavae and azygos veins appeared normal. Cardiotomy was performed and exploration of the right cardiac chambers revealed a flexible, competent tricuspid valve, no abnormal communications and no evidence of pulmonic or infundibular stenosis. Blood samples from the right atrium and right ventricle showed no increase in oxygen content over blood from the superior vena cava. A small irregular nodular lesion in the superior segment of the lower lobe of the right lung was resected and the presence of enlarged hilar lymph nodes compressing the right lower lobe bronchus was noted.

Microscopic examination of the atrial appendage revealed hypertrophy of muscle fibers. The resected pulmonary nodule was a granulomatous lesion compatible with tuberculosis.

A follow-up examination 5 years later showed no other evidence of heart disease and the subject's electrocardiogram was within normal limits (Fig. 1B).

Comment: This patient was completely asymptomatic and had no clinical, electrocardiographic or hemodynamic evidence of heart disease. The cardiac pathology apparently was limited to the unusual right atrium, which showed both dilatation and hypertrophy involving chiefly the atrial appendage.

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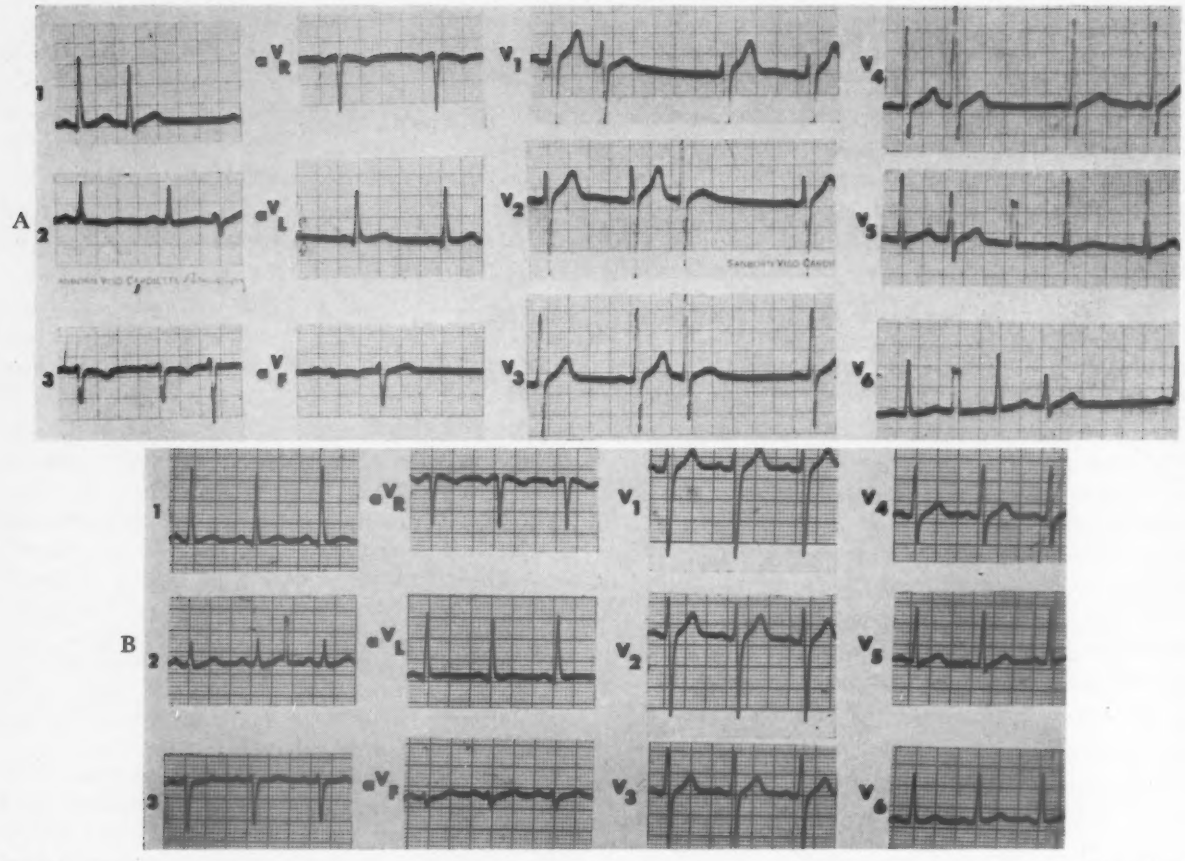
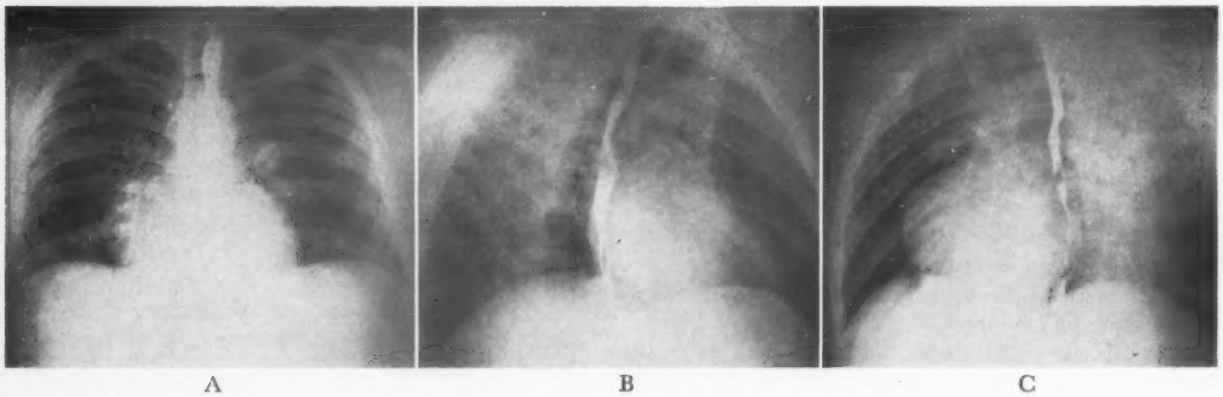


FIG. 1. Case 1. A, electrocardiogram taken on December 20, 1955, showing frequent atrial premature beats with aberrant ventricular conduction and slight flattening of some of the T waves. B, normal electrocardiogram taken on October 19, 1960, 5 years after exploratory cardiotomy.



A B C

FIG. 2. Case 1. Teleoroentgenograms of chest. A, posteroanterior projection showing prominent bulge on right border of heart. Remainder of cardiac silhouette is not remarkable. Note small rounded density in right midlung field. B, right anterior oblique projection. C, left anterior oblique projection.

CASE 2. A 21 year old man was first studied for heart disease during military service in 1951, after the discovery of a heart murmur. No specific diagnosis was established. Following his separation from the Army in 1952, he was asymptomatic until January 1954, at which time he was admitted to the Philadelphia Veterans Administration Hospital with a history of pain and swelling in the left foot of 4 days' duration, and dyspnea, cough and pain in the chest of 3 days' duration.

On admission, a marked pectus excavatum and pigeon breast deformity were noted. There was a pleural friction rub on the left anteriorly, a soft apical systolic murmur was heard, and there was tenderness of several joints, without redness or swelling. Leucocytosis and an increased erythrocyte



FIG. 3. Case 1. Posteroanterior planigram at 10 cm. from table top showing irregular lobulated mass inseparable from right cardiac border. Note small rounded density in right midlung field and compression of right lower main bronchus.

sedimentation rate were present. Two elevated antistreptolysin titers of 384 and 786 Todd units were reported on admission and a month later and the streptococcal antihyaluronidase titer on both occasions was 512.

Electrocardiograms revealed partial A-V heart block, the maximum duration of P-R intervals reaching 0.46 second (Fig. 4A). Transient abnormalities of the T waves were observed in serial records. The pattern showed progressive improvement to a normal configuration during his hospital stay (Fig. 4B).

Roentgenologic examination of the heart revealed no gross cardiac enlargement, but an unusual cardiac silhouette was present with a prominent bulge anteriorly and to the right (Fig. 5). The thoracic cage was deformed. Fluoroscopically the border showed pulsations synchronous with atrial contraction, but it could not be determined whether the atrium was enlarged or displaced by another chamber. Reference to records of previous hospitalization showed that this unusual cardiac silhouette had been noted previously. After study it had been concluded that it represented either a pericardial cyst or deformity due to adhesions from pleural disease in childhood. During the same hospitalization a bronchoscopic examination had shown a congenital anomaly of the right bronchial tree.

Course: A diagnosis of acute rheumatic fever was made, the patient was treated with salicylates and bed rest and after discharge a program of prophylactic penicillin therapy was instituted. He was seen again in 1959 for an acute exacerbation of chronic otitis media and acute tonsillitis. After recovery a tonsillectomy was performed. At this time attention was again directed to the deformed thoracic cage and to the bizarre configuration of the cardiac sil-

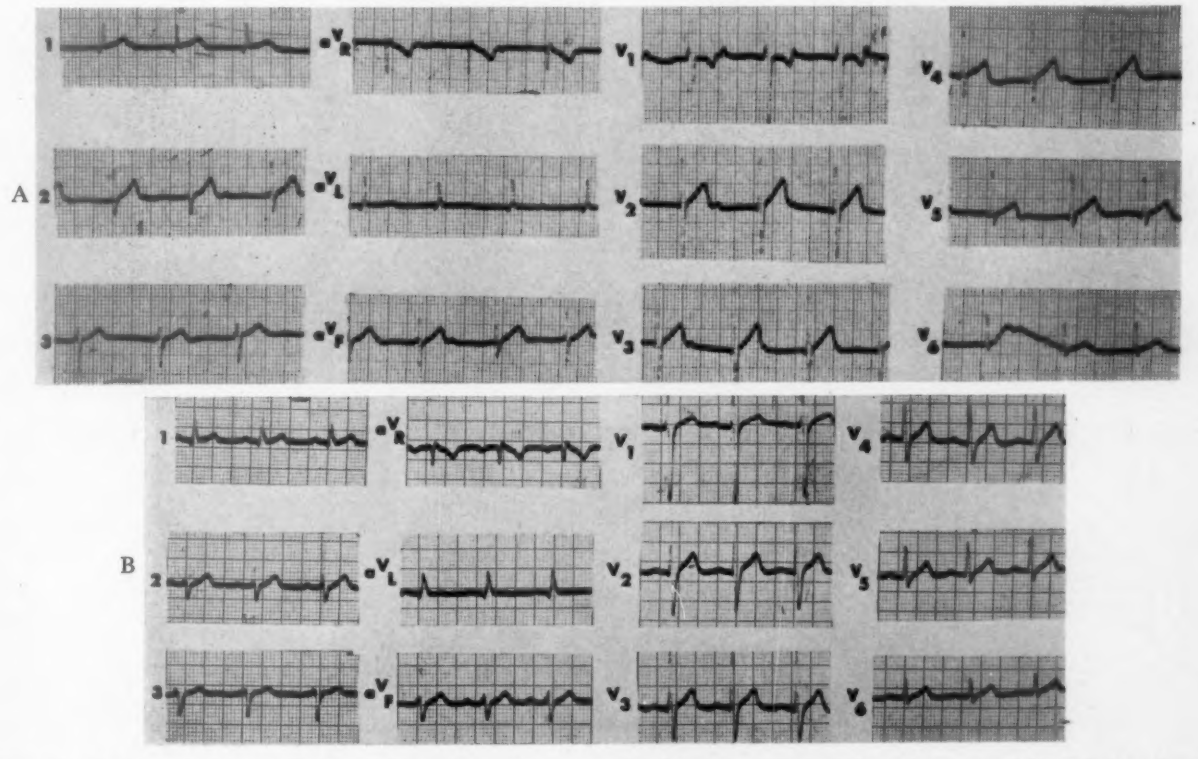
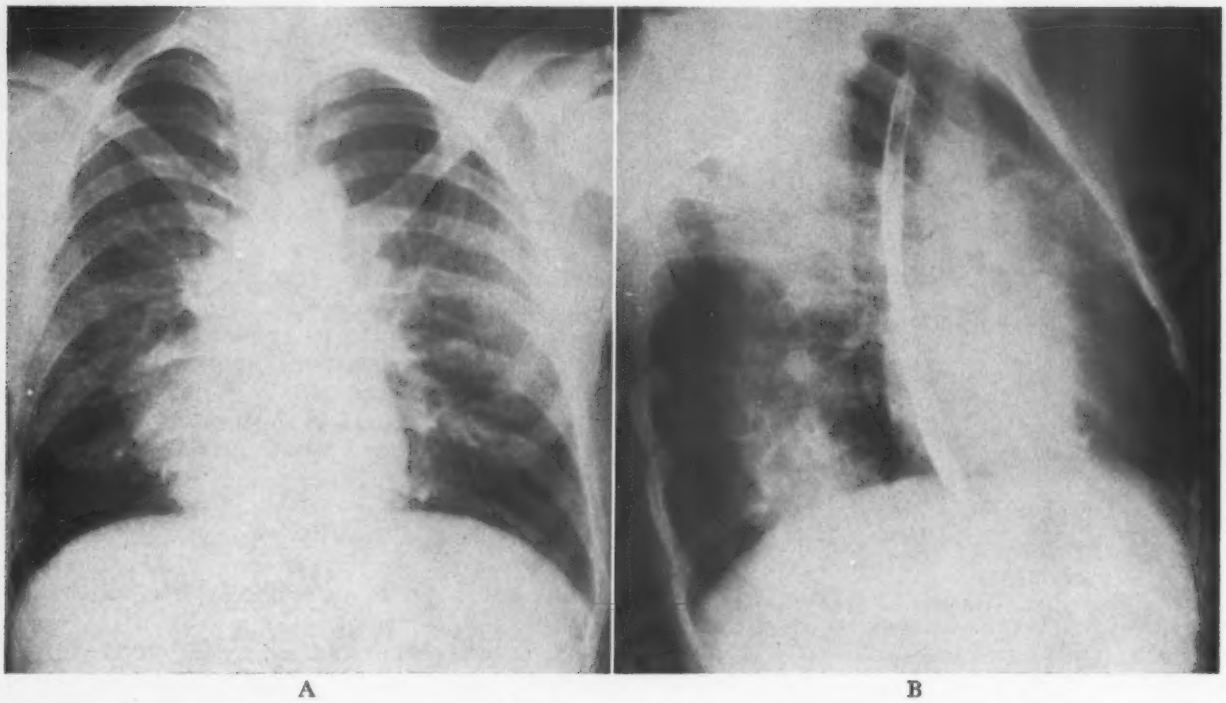


FIG. 4. Case 2. A, electrocardiogram taken on January 25, 1954, showing marked prolongation of P-R interval. B, electrocardiogram $2^1/_2$ months later (April 5, 1954) showing A-V conduction within normal limits.



A B

FIG. 5 A and B. Case 2. Teleoroentgenogram of chest. A, posteroanterior projection showing prominent bulge on right border of heart. B, right anterior oblique projection.

houette, which was unchanged since 1954. The first ribs were hypoplastic, and an anomalous configuration of the sternum was described, with an angulation of approximately 160° between the manubrium sterni and the gladiolus. A skeletal survey for other anomalies revealed slight scoliosis in the cervicodorsal region, accessory carpal bones adjacent to the ulna, and similar bony densities lateral to the elbow

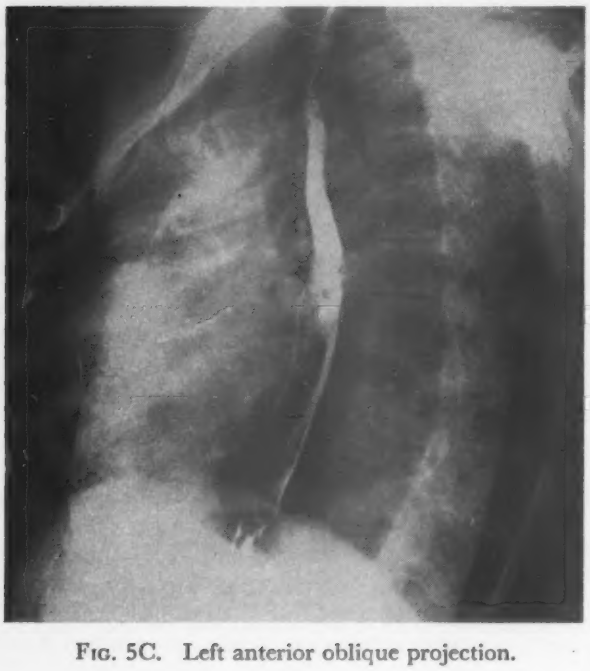


FIG. 5C. Left anterior oblique projection.

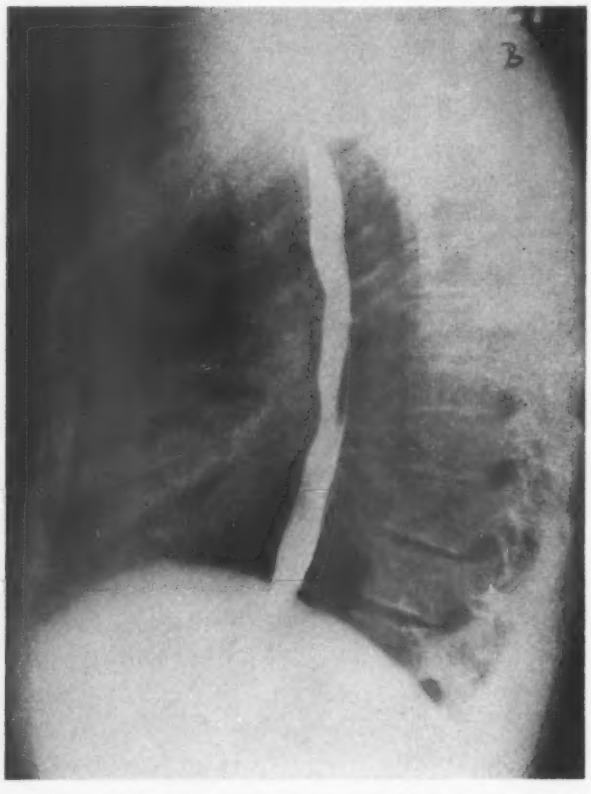


FIG. 5D. Left lateral projection showing the deformity of the chest wall.

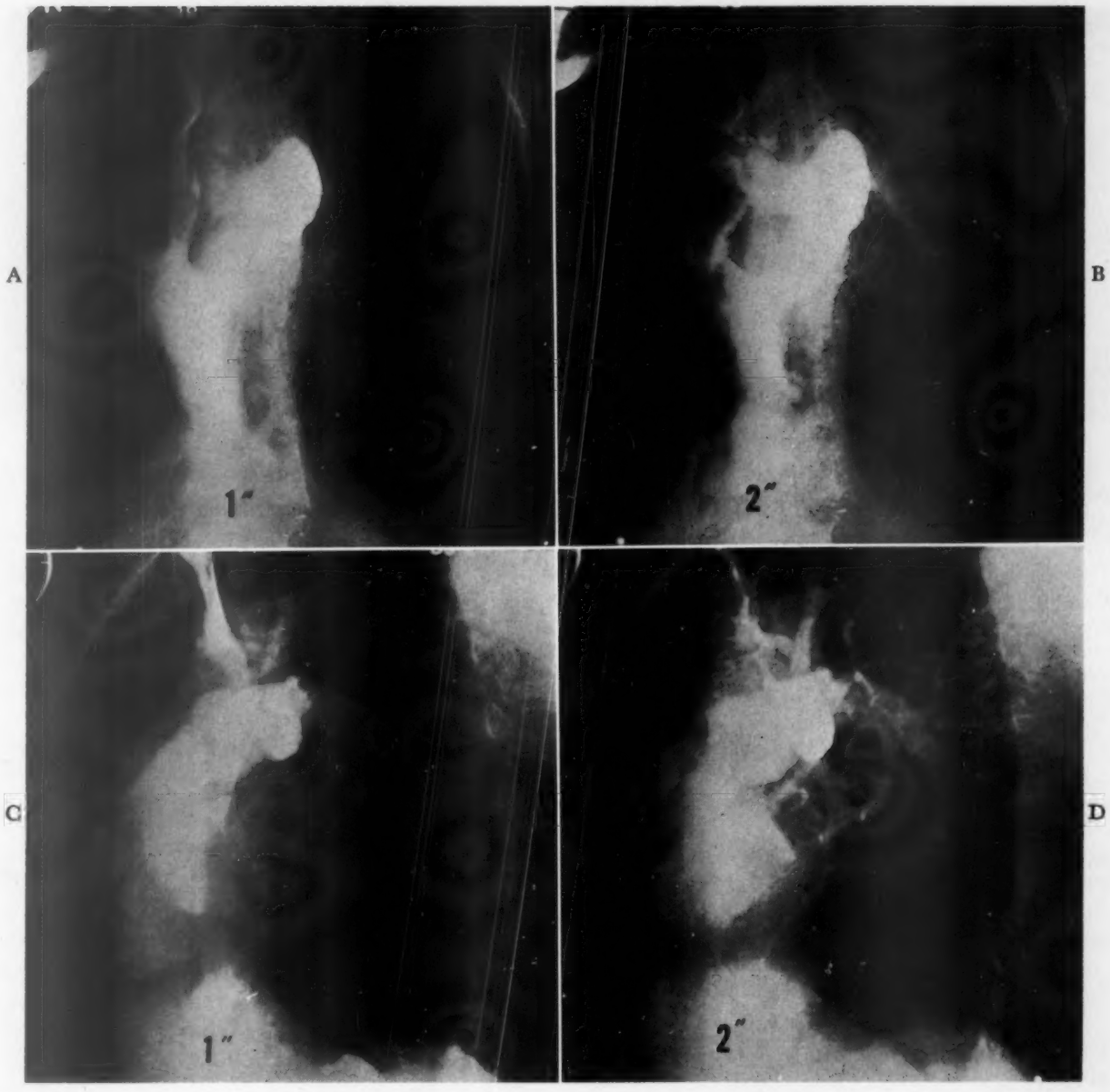


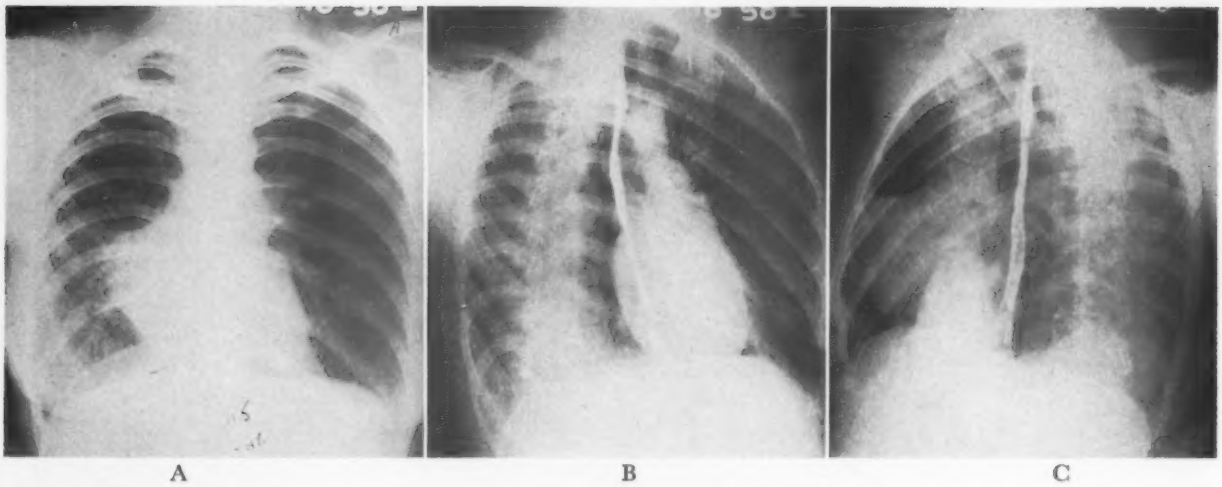
FIG. 6. Case 2. Angiocardiograms. A and B, posteroanterior angiocardiograms at 1 second and 2 seconds showing opacification of right cardiac chambers. Right atrium is markedly enlarged, particularly the atrial appendage. C and D, left anterior oblique angiocardiograms at 1 second and 2 seconds demonstrating large right atrium. The atrial appendage is particularly well seen in the 2 second film.

joints. The electrocardiogram was still within normal limits except for some prominence of P waves with no prolongation of the P-R interval.

An angiocardiogram (Fig. 6) revealed an enlarged right atrium with an exceptionally prominent atrial appendage and some thickening of the wall. The right ventricle, pulmonary arteries, left atrium and left ventricle were normal. It was concluded that the subject had a congenital anomaly of the right atrium, and the presence of several other congenital malformations confirmed this impression.

Comment: Although this patient had acute rheumatic fever in 1954, there was no antecedent history of rheumatic fever or rheumatic heart disease. The deformity of the cardiac silhouette was known to be present in 1951, at which time the only other abnormal cardiac finding was a soft, nondescript systolic murmur. Several other congenital malformations were present.

CASE 3. A 45 year old nurse had an unusual cardiac silhouette discovered on a routine roentgenogram of the chest (Fig. 7). The principal abnormality was a prominent bulge on the upper border of the right side of the heart, which had been attributed to an



A B C

FIG. 7. Case 3. Teleoroentgenograms of chest. A, posteroanterior projection showing prominent bulge on right border of heart. B, right anterior oblique projection. C, left anterior oblique projection.

"adhesion" deforming the border of the right atrium. Fluoroscopically the area in question showed expansile pulsation and could not be separated from the rest of the cardiac silhouette. She was asymptomatic, cardiac examination was not remarkable, and the electrocardiogram was within normal limits.

She refused to submit to any further studies, but the striking similarity to the cardiac silhouette in Case 2 is apparent.

Comment: Although no definitive studies were performed, the roentgenologic findings strongly suggest that the pathology is similar to that of the other two cases in which more accurate identification was possible.

COMMENTS

The subject of idiopathic cardiac hypertrophy has been reviewed at length by Rosenbaum.[4] Most of the reported cases either involved the left ventricle or showed diffuse cardiac enlargement. Idiopathic hypertrophy of the right side of the heart alone is rare, and in all of the reported cases the right ventricle and pulmonary arteries were enlarged. The electrocardiograms always showed a right axis deviation or right ventricular hypertrophy and all of the patients had significant cardiac symptoms. In the cases reported here the enlargement was chiefly of the right atrium, with normal electrocardiograms not reflecting any right ventricular preponderance.

The diagnosis of idiopathic hypertrophy has generally been made by the exclusion of all other possible causes for hypertrophy. It is quite likely that in many cases some obscure or yet unrecognized etiologic factor may exist. Rosenbaum[4] lists numerous hypotheses which have been advanced to account for idiopathic cardiac hypertrophy, including congenital anomalies, abnormal infiltrations of the heart, infections, metabolic disorders, diseases of other organs or systems and transient overloading of the heart with subsequent hypertrophy. Many of these etiologic factors can be excluded in the study of the individual patient and others are difficult to document.

Investigation of other similar cases with detailed hemodynamic studies may cast further light upon the subject. In the absence of evidence of such a hemodynamic abnormality, with no inflammatory process in the one resected atrial appendage, and without symptoms of antecedent heart disease, we consider a congenital abnormality of the atrium the most tenable diagnosis in our patients.

SUMMARY

Three cases of apparently massive isolated enlargement of the right atrium have been observed. A congenital malformation seems the most likely explanation in this series of cases.

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Rudimentary Left Coronary Artery*

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RARELY IS an anomaly of the coronary arteries suspected clinically in an essentially asymptomatic infant. During a study of the electrocardiograms of premature infants, an abnormal record suggested this diagnosis.

CASE REPORT

M. B. was a 900 gm. premature Negro male infant, with an estimated gestational age of 26 weeks. He was the product of an unsterile precipitous delivery. The infant was resuscitated by bulb suction after a 1 minute period of apnea. His condition at birth was fair, with a weak cry and a good heart beat. The mother was a 37 year old gravida VI, para V, abortus O, type O Rh+, VDRL negative; she had mild pre-eclampsia during this pregnancy. Two days prior to delivery she was admitted to the Grady Memorial Hospital for moderate, asymptomatic vaginal bleeding.

Physical examination of the infant on admission to the premature nursery showed him to have good color, some irregularity of respiration and moderate intercostal retraction. The lungs were fairly well aerated and cardiac examination was unremarkable.

During the first 24 hours of life the infant was in satisfactory condition in an Isolette with 35 per cent oxygen; penicillin and streptomycin were administered as prophylaxis. A routine electrocardiogram (Fig. 1) taken during the first 24 hours of life showed a left bundle branch block pattern and no evidence of atrial activity. The diagnosis of an anomaly of the coronary arteries was suggested. On the second day of life he became cyanotic, with barely perceptible respiration. He was placed in a Bloxom respirator and caffeine was administered without apparent effect; the infant died 18 hours thereafter.

Postmortem examination showed the significant pathology to be confined to the cardiopulmonary system. The heart weighed 2 gm., and the atria, ventricles and valves appeared normal. There was a patent foramen ovale and a patent ductus arteriosus. On gross examination, the coronary ostia were not remarkable and there was agenesis of the anterior descending branch of the left coronary artery; the circumflex branch of the left coronary artery was atretic, terminating 10 mm. from its origin (Fig. 2). The lungs showed atelectasis neonatorum.

Histologic examination of the myocardium showed rudimentary left coronary vessels, despite their absence on gross inspection. There were multicentric foci of ischemic injury—petechial hemorrhages into the myocardium and fragmentation of myocardiocytes with dissolution of the finer cytoplasmic structure (Fig. 3). Little difference was noted between the changes in the right and left ventricles, although these changes were best developed in the right ventricle.

COMMENTS

Gray's[1] description of coronary artery anomalies best summarizes the approximately 100 cases of this condition reported in the literature: "The left coronary artery or its descending branch may arise from the left pulmonary artery, supplying the left ventricle. This anomaly can be diagnosed clinically and usually

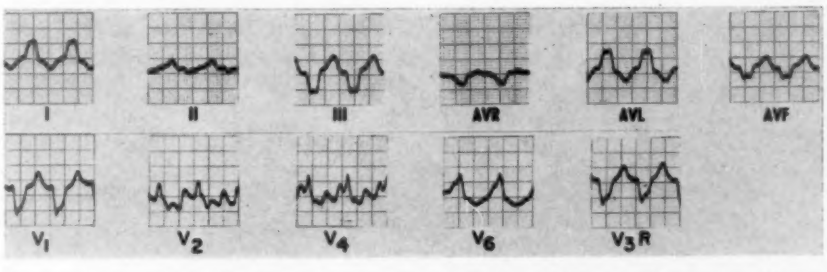


FIG. 1. Electrocardiogram taken on the first day of life, showing no evidence of atrial activity, and a left bundle branch block pattern.

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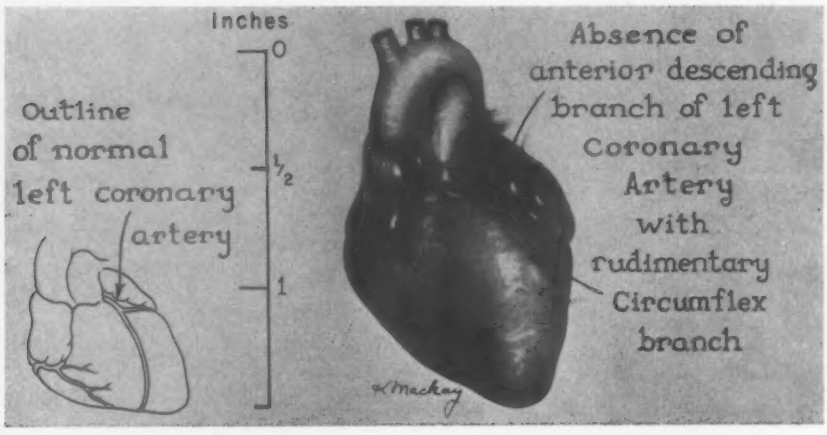


FIG. 2. Agenesis of the anterior descending branch of the left coronary artery and atresia of the circumflex branch of the left coronary artery in a heart weighing 2 gm.

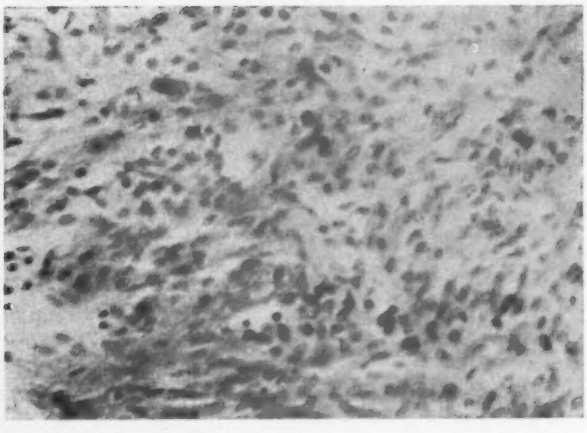


FIG. 3. Myocardium, showing focus of ischemic injury (original magnification, × 230).

leads to death in infancy. Rarely both coronaries arise from the pulmonary artery. Single coronary arteries have been described. The left coronary may be a branch of the right or both arteries may arise in the same aortic sinus. There may be three coronary arteries, the accessory supplying part of the branches of either artery." Gould[2] lists no additional variations of the coronary arteries. We know of no previously reported case of a rudimentary left coronary artery.

SUMMARY

A rather unique cardiac anomaly, a rudimentary left coronary artery, has been described, with electrocardiographic and pathologic correlation. The presence of left bundle branch block was an important clinical sign. The cardiac anomaly was the presumptive cause of death.

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Diagnostic Shelf

Electrocardiographic Changes Noted at the Onset of Coronary Occlusion and Myocardial Infarction*

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ONLY ON rare occasions is there an opportunity to record electrocardiographic observations at the very onset of coronary occlusion and myocardial infarction. Such an occasion was presented when one of my colleagues sustained an acute myocardial infarction the day following an annual physical examination. The findings were of sufficient interest to prompt this report.

CASE REPORT

Day Prior to Attack: This 54 year old physician presented himself for annual physical examination. He was asymptomatic with the exception of occasional cramps in the calves of both legs observed following unaccustomed physical activity. Physical examination revealed a healthy-appearing white man, 67 inches tall, weighting 169 pounds. The blood pressure was 116/72 mm. Hg and the pulse was 60 per minute and regular with occasional premature contractions noted. Absence of pulsations of both dorsalis pedis pulses were noted. The posterior tibial pulsations were good. There were no other significant findings. The x-ray film of the chest was within normal limits. A routine twelve lead electrocardiogram was normal with the exception of one ventricular premature contraction (Fig. 1).

First Day of Illness: The following morning at 9:30 A.M. the patient felt substernal pressure and began sweating. He entered my office which was close by and stated that he felt that he was having angina. On noting the patient's general appearance and the sweat on the brow, it was assumed that the episode probably represented more than simple angina, particularly because no previous anginal dis-

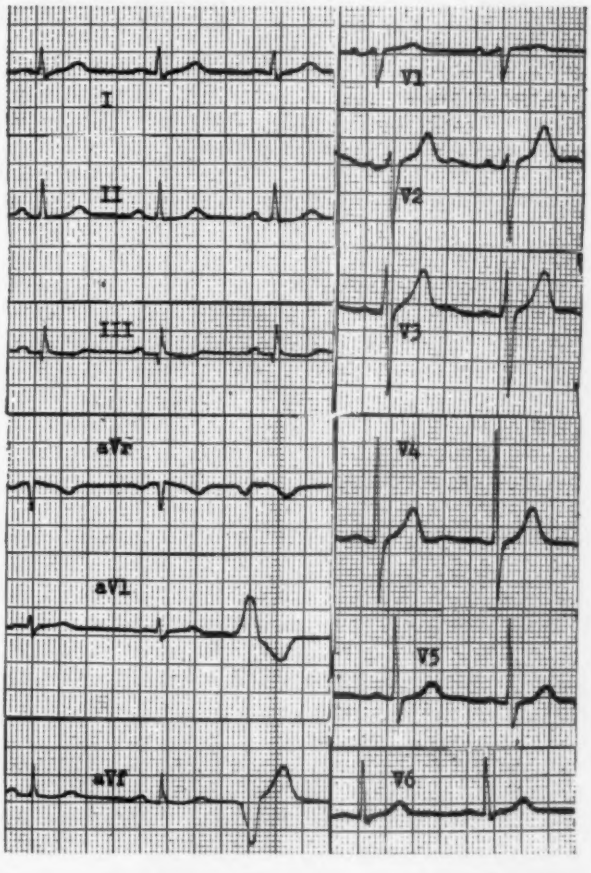


FIG. 1. One day before attack. A normal electrocardiogram, essentially unchanged from previous annual tracings obtained for 15 years. A rudimentary r wave is present in lead III. There is one ventricular premature contraction recorded simultaneously in leads aVR, aVL and aVF.

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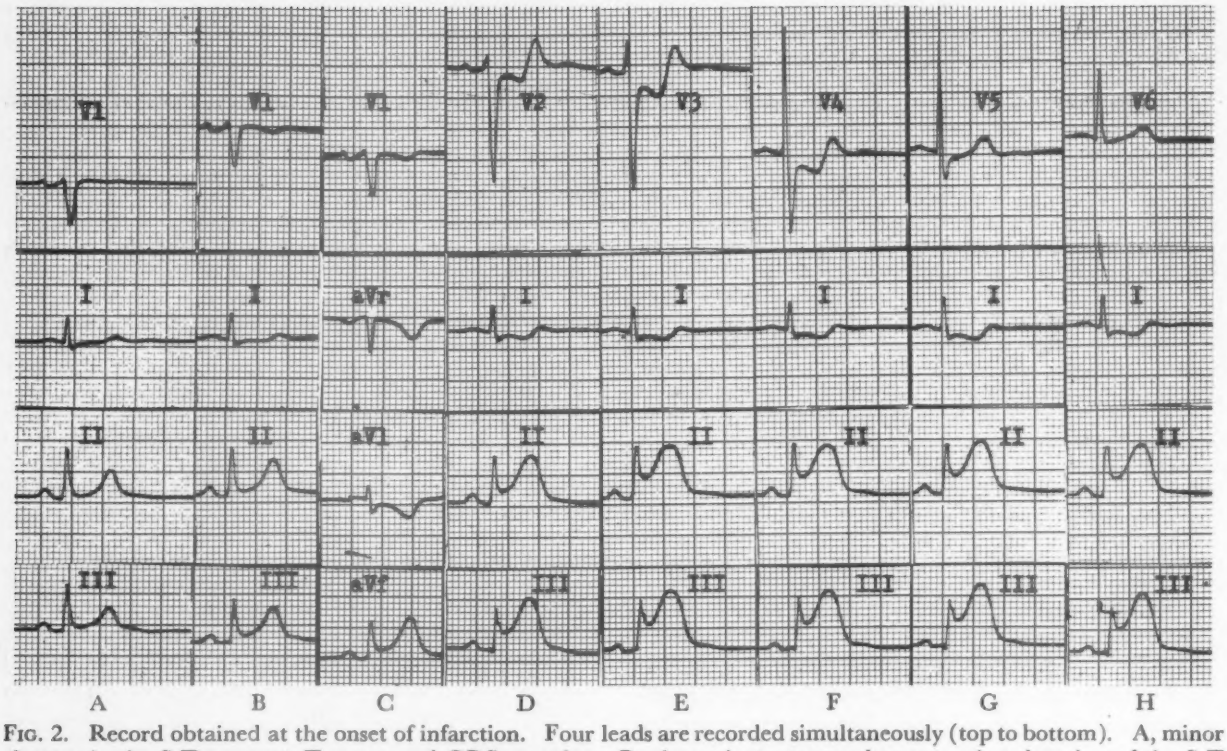


FIG. 2. Record obtained at the onset of infarction. Four leads are recorded simultaneously (top to bottom). A, minor changes in the S-T segment, T waves and QRS complex. B, almost instantaneously progressive elevation of the S-T segments in leads II and III. C, leads aVR, aVL and aVF show compatible changes. The T wave in V_1 is inverted. D, progressive changes in the S-T segment. Lead V_2 shows significant S-T segment depression. E–H, persistent S-T segment changes with S-T depression in the precordial leads.

comfort had ever been observed by the patient. By this time he complained of mild discomfort in the left arm as well as in the chest. The blood pressure was 120/80 and the pulse was 64 per minute. The cardiac sounds were unchanged. An electrocardiogram taken immediately on a four channel recorder showed minimal changes in the S-T segment. As the recording continued, marked S-T segment changes developed rapidly (Fig. 2). By the time the routine twelve lead electrocardiogram had been completed, a marked change in the S-T segments in the three standard limb leads had occurred. The changes were consistent with an injury current of the inferior and posterior wall of the myocardium.

The patient was transferred immediately by stretcher to the hospital which was located next door. Initial laboratory studies demonstrated a white blood cell count of 13,400 per cu. mm. with 63 segmented cells; hemoglobin, 15.3 gm. per 100 ml.; erythrocyte sedimentation rate, 13 mm. per hour; transaminase, 25 units; blood sugar, 121.6 mg. per cent; prothrombin time, 15 seconds. The discomfort in the chest was easily controlled with minimal amounts of morphine. At 2:00 P.M. periods of marked bradycardia were noted and the electrocardiogram at that time showed transitory periods of slowing of the cardiac rate to 30 per minute. Further evolutionary changes in the electrocardiogram were also noted including a change in QRS configuration compatible with a change in intraventricular conduction (Fig. 3). Because of the serious implications of periods of bradycardia in the face of acute myocardial infarction, atropine, 0.6 mg., was given intravenously. After this initial dose, the atropine was repeated by intramuscular injection whenever the cardiac rate dropped to 60 or below. Within the first 24 hours 4.8 mg. of atropine were required to maintain the pulse rate at the desired level. The blood pressure remained relatively normal, dropping as low as 98/64 mm. Hg.

Second Day: The electrocardiogram showed marked evolution of the acute infarction pattern with almost complete disappearance of S-T segment elevation (Fig. 4). The cardiac rate was 75 per minute and regular. The serum transaminase was 237 units. Atropine was discontinued and Banthine® 50 mg. every 6 hours was administered.

Third Hospital Day: The patient was asymptomatic. The serum transaminase was 110 units. The electrocardiogram showed further leftward rotation of the T vector with further inversion of the T wave in lead II. The S-T segments had returned nearly to the baseline and this particular electrocardiographic pattern remained unchanged from that date.

Subsequent Course: There was no other change in the patient's condition. The serum transaminase rapidly dropped to 30 units. After 6 weeks of hospitalization and gradual ambulation he was returned to his home for convalescence.

After a suitable period of convalescence he resumed

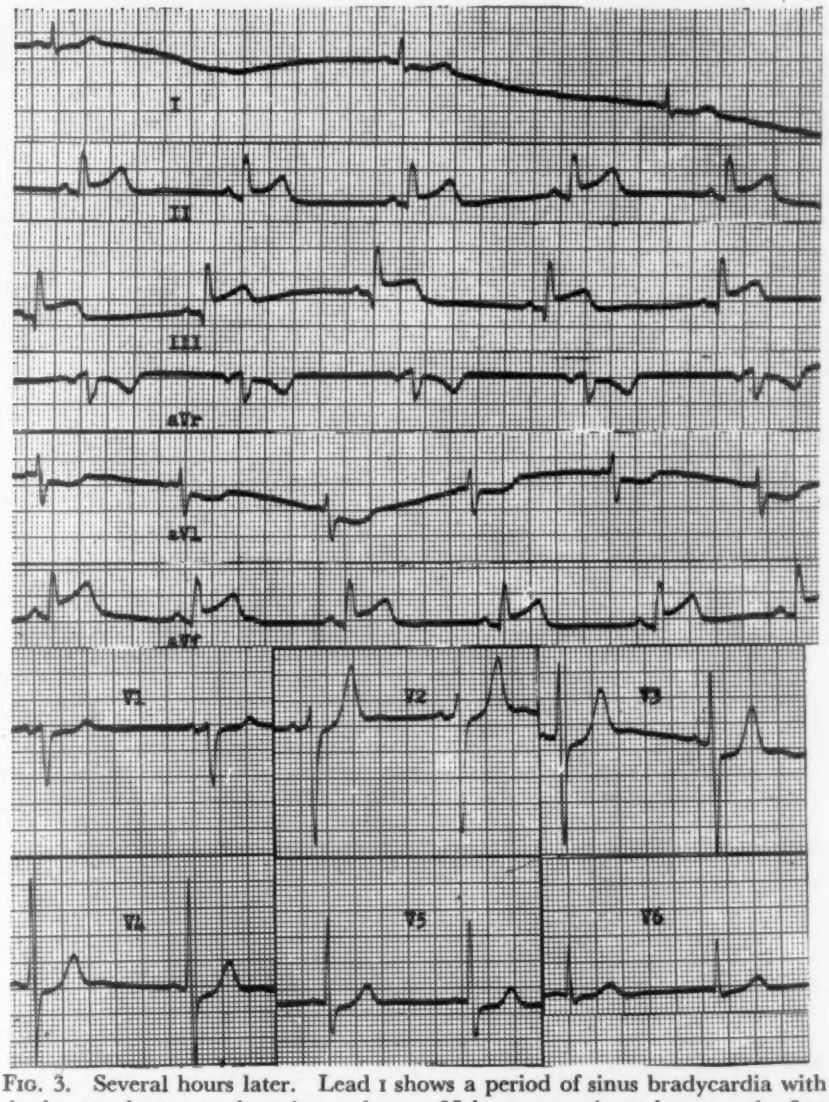


FIG. 3. Several hours later. Lead I shows a period of sinus bradycardia with the beat to beat rate dropping as low as 25 beats per minute between the first two complexes. The duration of the QRS complex is within normal limits but it is definitely increased over the duration in the preinfarction record. Note the blunting of the apex of the R wave in leads II, III and aVF and the development of Q waves in those leads. The high take-off of the S-T segment is not nearly so marked as noted at the onset of infarction.

the full activities of his professional life without complications. The cardiac size on x-ray film showed no changes before and after myocardial infarction. Although he is a vigorous man with a keen interest in outdoor sports and activities, he has never experienced anginal discomfort. Over 4 years have elapsed since the initial episode of acute myocardial infarction during which time his only regimen has included recommended weight reduction, regular physical activity and no medications.

COMMENTS

S-T Changes at Onset of Infarction: There are several interesting features to this case. By virtue of the electrocardiogram recorded the day prior to the onset of infarction and the normal transaminase level recorded at the onset of the attack, the actual time of occurrence of coronary occlusion can be relatively well pinpointed. It is of some interest that the electrocardiographic changes noted consisted primarily of S-T segment changes at the onset of occlusion. This is somewhat at variance with the classic concept of T wave changes followed by S-T segment and QRS changes. It should be recalled that the classic experimental approach to ligation of the coronary arteries is not necessarily analogous to the course of events to be encountered during clinical in-

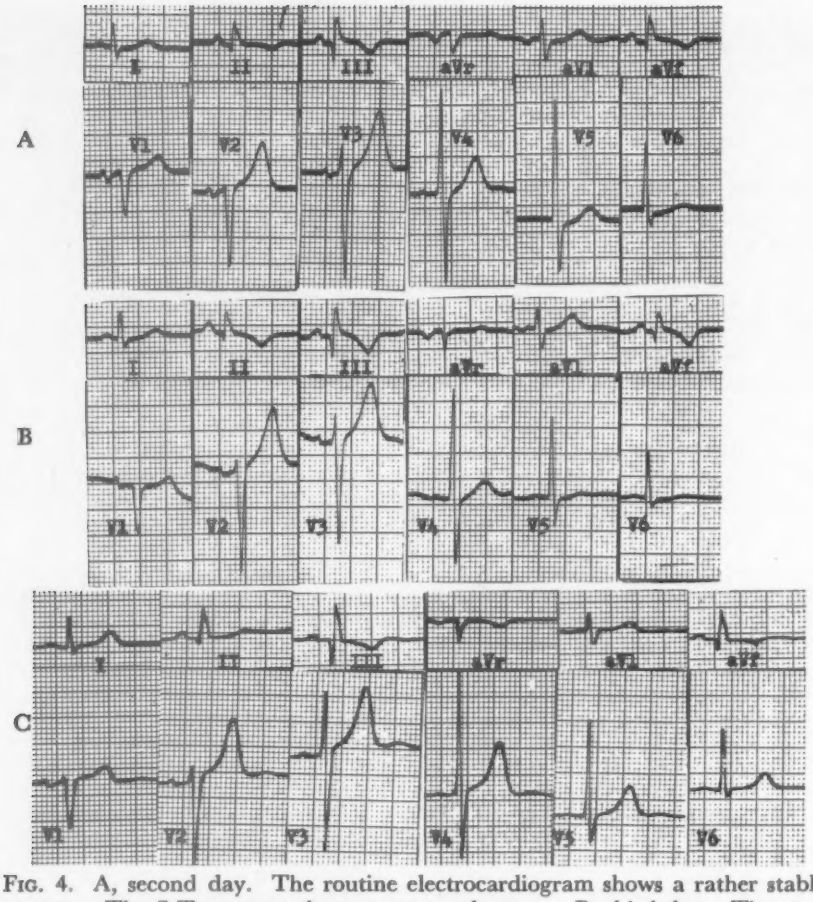
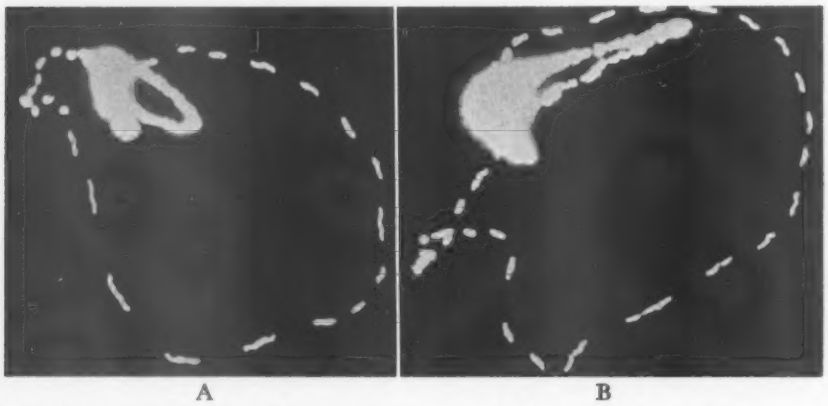


FIG. 4. A, second day. The routine electrocardiogram shows a rather stable pattern. The S-T segment changes are nearly gone. B, third day. The routine electrocardiogram presents stable pattern. The complete evolution of the electrocardiographic changes occurred within 3 days. C, 4 years after infarction. The record is unchanged with the exception of rotation of the T vector (T in lead II is now upright).



A B

FIG. 5. Vectorcardiograms (frontal plane). A, preinfarction vectorcardiogram. B, postinfarction vectorcardiogram.

farction.[1] The changes noted during the acute infarction suggest that more attention should be given to the S-T segment changes of acute myocardial infarction than has been noted in the past. It has previously been well documented that T waves may be strongly positive in the leads in which they are expected to be negative at the onset of acute myocardial infarction; however, very little attention has been given to the acute changes of the S-T segments.[2-3]

Another interesting feature in the electro-

cardiographic picture in this case is the rapid subsidence of the elevation of the S-T segments and with their disappearance the expected inversion of the T wave was noted. The electrocardiogram became stable very early in the course of the acute illness.

Intraventricular Conduction Disturbance: A third feature of some interest is the development of an obvious intraventricular conduction defect which can only be ascertained with certainty by comparing the infarction record to the pre-infarction record obtained at the time of annual physical examination. This suggests the possibility that the Q wave changes of inferior wall myocardial infarction may be related to an abnormality in conduction rather than specifically to an area of significant myocardial necrosis. The rapid rise and fall of the transaminase determinations parallel but follow the rapid rise and quick subsidence of the S-T segments.

A vectorcardiogram recorded the day prior to the infarction and a subsequent one obtained in the postinfarction period provided an opportunity for comparison of serial changes in the vectorcardiogram due to infarction (Fig. 5). The entire QRS loop was rotated in a counterclockwise fashion in the frontal plane projection. The loop was deformed at its base, supporting the thesis that the infarction was located at the base of the ventricle. The T loop was altered in configuration and rotated upward.

Bradycardia and Vagotonia: Still another feature of clinical importance in this case is the observation of significant bradycardia at the time of myocardial infarction. Such reactions are the result of vagal reflexes, probably stimulated by ischemic areas in the myocardium. Vagotonic drugs are commonly used in treatment of myocardial infarction which include morphine and quinidine. Administration of vagolytic medications such as large doses of atropine as an acute measure and maintenance of vagolytic medications such as Banthine or Pro-Banthine® is indicated in the presence of bradycardia. The relatively slow cardiac rates usher in the opportunity for serious ventricular arrhythmias or cardioinhibitory responses with circulatory shock. Their early recognition and treatment can be life-saving. Larger doses of atropine than given in this case can be used. In this case it was elected to give relatively moderate doses at frequent intervals. There is some evidence to support the thesis that atropine-like drugs augment coronary circulation in the presence of coronary occlusion.[4]

Summary

A case of acute myocardial infarction demonstrating the early onset of the evolutionary changes in the electrocardiogram with some unusual features has been presented. An electrocardiogram was recorded one day prior to myocardial infarction. The onset of pain in the chest was associated with the rapid development of marked S-T segment changes. The progressive development of the changes was recorded at the onset of pain in the chest. A change in intraventricular conduction resulting in an inferior wall infarction pattern could be detected by comparing the serial changes with the pre-infarction record. Marked sinus bradycardia also occurred during the first day of illness. Comments relative to the management of the bradycardia associated with acute myocardial infarction are included.

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Seminar on the Role of Salt in Cardiovascular Hypertension (Part I)

Foreword

THE CONTENTS of this seminar represent the proceedings of a symposium on "The Role of Salt in Cardiovascular Hypertension" held at the College of Medicine of The University of Florida on January 19, 20 and 21, 1961. It was the aim of this symposium to cover thoroughly a restricted area of the field of cardiovascular hypertension. The time seemed propitious for a discussion of the role played by salt in hypertension because a number of investigators have been able to induce hypertension when salt is given in excess quantities to experimental animals. Others have demonstrated that salt "sensitizes" rats to the hypertensive effects of certain pressor agents such as desoxycorticosterone acetate or to the hypertension induced by a regenerating adrenal gland. Salt may or may not be a common denominator among the various types of hypertension but it cannot be denied that this agent alone is capable of producing hypertension whether administered in food or in drinking water. It seems certain that a better understanding of the physiologic function of sodium and the other inorganic ions of the body is necessary before an understanding of the etiology of hypertension will be possible.

A program of this kind could not be planned and executed without financial support. This was generously provided by the Merck Sharp and Dohme Postgraduate Program.

Encouragement and administrative support were given without reservation at every level of the university. Many of my colleagues contributed generously of their time. I am particularly grateful to Drs. Arthur B. Otis, Wendell N. Stainsby and Lamar Crevasse.

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Changes in Blood Pressure and Body Sodium of Rats Fed Sodium and Potassium Chloride*

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THERE ARE innumerable references to salts of sodium and potassium in the ancient literature. As long as 4,000 years ago a Sumerian physician, in a baked clay tablet, recommended inclusion of potassium nitrate in a number of prescriptions.[1] Scientific knowledge of sodium and potassium cannot, however, antedate the first decade of the nineteenth century for it was in that decade these were first recognized as elements by the electrochemical researches of Sir Humphrey Davy. For long in the medical literature it was customary to attribute to Schmidt and his work on cholera[2] about 1850 the first research on sodium in medicine. Gamble[3] in 1953, however, was able to show that that honor belonged to one W. B. O'Shaughnessy, M.D., who published in 1831 the first treatise on the subject.[4]

Chapman[5] has traced the history of these matters to the earliest known reference to a fall in elevated blood pressure when sodium chloride was withheld to Ambard and Beaujard in 1904. Perhaps one should mention Wallace's[6] address to the London Vegetarian Society in 1893. Dr. Priddle was kind enough to make a copy of this magnificent document available to us. Certainly, one should also mention Von Bunge's[7] studies of the sodium-potassium interrelationship during the last half of the nineteenth century. Much thought was then given to the difference between the carnivorous diet and the herbivorous diet as to their relative and absolute amounts of sodium and potassium. The real difference was determined by direct chemical analysis in 1843. It had, prior to that, been supposed the herbivores went to salt licks to get extra sodium chloride and the carnivores obtained their salt from the herbivores. In fact, there is just as much sodium in the herbivorous diet as in the carnivorous but there is a tremendous difference in the potassium content. A carnivore gets perhaps four or five times as much potassium as sodium in his diet while an herbivore gets twelve to twenty times as much. It was speculated that the real reason the herbivore sought out salt licks was to obtain some extra sodium to balance his high intake of potassium. The herbivore-carnivore-salt lick matter has been discussed, investigated and rediscussed so many times and so much it is a stale affair indeed. Perhaps the less said about it the better. We should not pass beyond it, however, without recognizing that, in nature, there is a relatively small amount of sodium in *any* diet and that there is much more potassium than sodium in *all* natural diets. There is an extensive literature[8] evidencing that many peoples have lived healthy lives for generations without adding sodium chloride to their food and the low human need for sodium has been amply shown experimentally, as I am sure Lewis Dahl will bring out in his presentation in this seminar.

Perhaps the next step was Allen's recommendation[9] in 1920 that salt be withheld from patients with hypertension. Verbal reports of Allen's findings were known much earlier among practitioners near New York. The senior author's father was a victim of hypertensive cardiovascular disease and he was treated by salt restriction. He died in 1922, the year of Allen and Sherrill's report[10] on the subject. The next move forward seems to be the observation of Priddle[11] published in 1931 that some patients with hypertension respond favorably to the administration of

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potassium salts. Next come the fascinating investigations of Thompson and McQuarrie[12] on the effects of various salts on carbohydrate metabolism and blood pressure in diabetic children.

So far as we have been able to determine, the first animal experimental evidence of the role of salt in hypertension is the investigation of Grollman, Harrison and Williams[13] at Vanderbilt University and Johns Hopkins reported in 1940 showing that various sterols were hypertensigenic only if additional salt were provided in the diet. Selye, Hall and Rowley[14] in 1943 and Knowlton et al.[15] demonstrated the effectiveness of desoxycorticosterone acetate in producing hypertension with the addition of extra sodium chloride. Lenel, Katz and Rodbard[16] produced hypertension in the chicken with hypertonic saline as the sole source of liquid as well as with 8 per cent sodium chloride feeding. Sapirstein, Brandt and Drury[17] in 1950 did so with hypertonic saline in the rat and Fukuda[18] in the rabbit in 1951.

Meanwhile, in the early 1940's Kempner[19] introduced the rice diet for treatment of hypertension. This diet should more properly be called the rice-fruit diet. It is not only low in sodium but also high in potassium.

In 1951 we began our investigations showing extra dietary sodium chloride without limitation of fluid was hypertensigenic in the rat. We now know that Dahl had made similar investigations beginning at about the same time but pressure of other duties and his move from the Rockefeller Institute to Brookhaven prevented his publishing his observations. One of the earliest studies of salt feeding in a normal human subject was that of McDonough.[20] In this same year, 1954, Dahl and Love[21] published their first report on the relation of sodium intake to essential hypertension in human subjects. This was, we believe, the first human evidence that salt might be a cause of hypertension.

The hypertension observed in human beings and experimentally induced hypertension in animals have often been linked with changes in tissue electrolyte and fluid compartments. Increases in extracellular volume or in tissue sodium have been reported in animals made hypertensive by various experimental procedures.[22–27] However, others have reported water and electrolyte concentrations within normal limits in tissues of animals with induced hypertension.[28] The exact relationship between hypertension and alterations in electrolyte metabolism remains unknown.

We have studied[29] the effects of high intakes of sodium chloride on the rat and have noted hypertension occurs rather consistently. The rise in blood pressure is proportional to the amount of dietary sodium chloride. If potassium chloride is added to diets containing large amounts of sodium chloride, some protection is afforded against the shortened life span and the hypertension of sodium chloride toxicity.[30] A recent study[31] revealed that total body sodium was increased in rats after eight months on diets containing high levels of sodium but animals fed diets containing equivalent amounts of sodium supplemented with potassium had normal amounts of body sodium and lower blood pressures. Since hypertension and increased body sodium existed in one group of animals whereas in the second group blood pressures were significantly lower and body sodium normal it was of interest to determine whether the hypertension and alteration in sodium developed concurrently.

In these experiments blood pressure and exchangeable body sodium were measured in three groups of rats: controls, those fed 9.8 per cent sodium chloride, and those given 9.8 per cent sodium chloride with sufficient potassium chloride to maintain a dietary ratio of one. When significant elevation of blood pressure developed in the group fed 9.8 per cent sodium chloride, a final estimate of exchangeable sodium was made, the animals were killed, sodium was measured in muscle and heart, and total sodium measured in the carcass.

Methods

Thirty day old male albino rats of the Sprague-Dawley strain were placed on the experimental diets and were kept in a constant temperature room (27°C.) with free access to distilled water. All animals received the same basal diet, the composition of which has already been described.[32] The only variable was the amount of sodium and potassium chloride. The control group was fed a diet containing 1.1 per cent sodium chloride and 0.66 per cent potassium chloride; the dietary ratio of sodium to potassium was approximately one. The "high Na" group was fed a diet containing 9.8 per cent sodium chloride and 0.6 per cent potassium chloride; the dietary ratio of sodium to potassium was 13. The "high Na + K" group received a diet containing 9.8 per cent sodium chloride and 6.1 per cent potassium chloride; the dietary ratio of sodium to potassium was one just as in the control group.

Each group consisted of fifteen rats. Systolic blood pressure was measured at frequent intervals by the cuff method of Kersten, Brosene and Ablondi.[33]

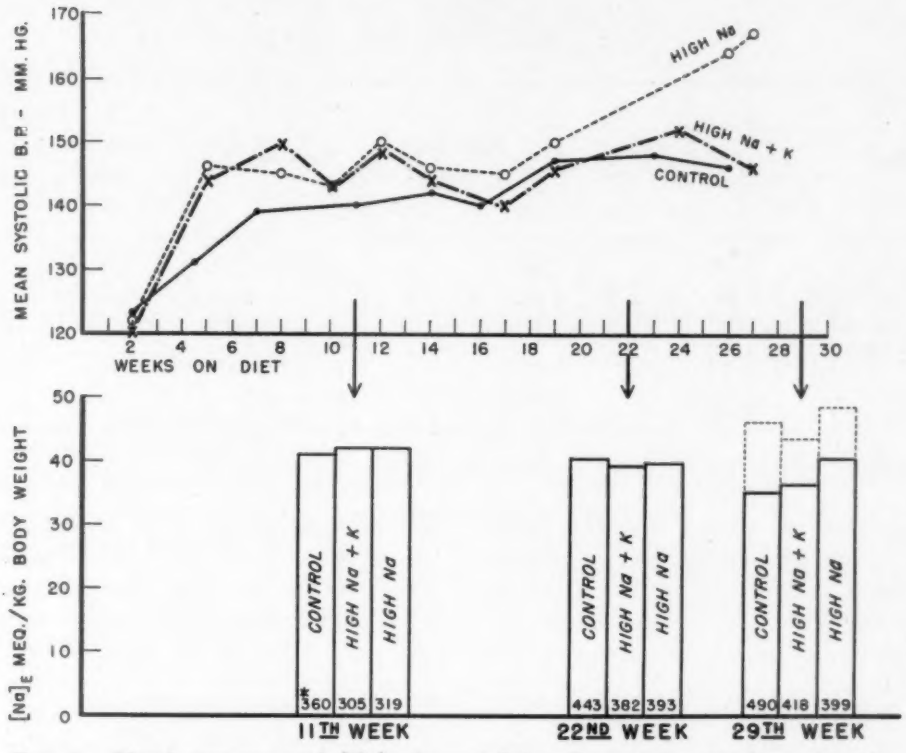


FIG. 1. Blood pressure and $(Na)_E$ in rats fed sodium and potassium chloride. Dotted area of bar graph at twenty-ninth week represents mEq. $(Na)_E$ per kg. *lean* body weight. * Average body weight in grams.

Exchangeable body sodium was determined in ten animals from each experimental group after 11, 22 and 29 weeks on the experimental rations. The procedures used for determination of exchangeable sodium [hereafter indicated by $(Na)_E$], tissue and carcass analyses are reported in detail in a later paper in this seminar.[10] Briefly, $(Na)_E$ was measured by the principle of isotope dilution using Na^{22} rather than Na^{24} as in previous studies. Each rat was given approximately 5 μc. of $Na^{22}Cl$ by intraperitoneal injection and an equilibration period of 18 hours was used. Urine samples were collected from the time of injection until 6 hours later and from 6 hours to 18 hours postinjection. $(Na)_E$ was calculated from the specific activity of the 6 to 18 hour urine sample. Urine was used because repeated bleeding of the rats in order to obtain serum samples was inadvisable. At the conclusion of the experiments blood was drawn, specific activity of both urine and serum were determined on each animal and used to calculate $(Na)_E$. The good agreement between $(Na)_E$ calculated from both serum and urine samples for the three groups is shown in Table I.

Total body sodium [indicated hereafter as $(Na)_T$] was measured with a Coleman Flame Photometer on a nitric acid digest of the homogenized carcass of the rat. Sodium was also determined by flame photometry on serum, urine and on nitric acid digests of skeletal muscle from the right hind legs and ventricular muscle. Water content, expressed as per cent of fresh tissue weight, was estimated by difference between fresh and dry tissue weights. The fat content of each carcass was calculated by difference after extraction of the homogenized carcass with anhydrous ethyl ether. Lean body weight was calculated by subtracting the weight of the fat from the whole body weight. The final determination of $(Na)_E$ was calculated as milliquivalent per kilogram of lean body weight because of the variation in fat content between the control and experimental rats.

RESULTS

The average values for systolic bood pressures are shown in Figure 1; measurements of

TABLE I

Exchangeable Sodium Calculated from Specific Activity of Both Plasma and Urine

Group	No. of Rats	$(Na)_E$ (mEq./kg. LBW*)	
		Based on Plasma	Based on Urine
Control	10	44.6 ± 0.58†	46.1 ± 0.46
High Na	9	47.2 ± 0.90	48.5 ± 0.89
High Na + K	10	43.0 ± 0.55	43.3 ± 0.83

* LBW = lean body weight.
† Standard error.

TABLE II
Exchangeable and Total Body Sodium

Findings	Control ± S.E.M.	High Na ± S.E.M.	High Na + K	Difference	
				High Na−Control	High Na−High Na + K
No. of rats	10	10	10		
$(Na)_E$ (mEq./kg. LBW)	46.1 ± 0.46	48.5 ± 0.89*	43.3 ± 0.83	2.4<0.03	5.2<0.001
$(Na)_T$ (mEq./kg. LBW)	53.7 ± 1.33	59.1 ± 1.10	55.5 ± 0.90	5.4<0.01	3.6<0.02
Average body weight	490	399	418	...	...
Fat (%)	24.0	15.5	16.2	...	...
LBW (%)	76.0	84.5	83.8	...	...

* For the experiment with $(Na)_E$ the number of rats was only nine instead of ten.

$(Na)_E$ are indicated by arrows and the mean values for $(Na)_E$ represented by the bar graphs. The average body weights of the three groups are shown at the time $(Na)_E$ was measured. The last set of bar graphs indicate milliequivalents of sodium per kilogram of lean body weight. It would have been preferable to express all measurements of sodium in terms of lean body weight but this was impossible since we were unable to estimate lean body mass in the living rats. However, it will be noted that the body weights of the two experimental groups were practically equal at all times which makes it unlikely that there could have been significant differences in the body position of these two groups. The body weights of the controls were 10 to 15 per cent higher than that of the experimental rats when $(Na)_E$ was measured at 11 and 22 weeks.

Blood Pressure: The blood pressures of the three groups were equivalent at the start of the experiment. After 4 weeks on the diets the two experimental groups showed an equal elevation of blood pressure over the control group. By the eighth week the blood pressure was significantly higher ($p < 0.05$) in rats receiving high sodium and potassium than in rats fed only high sodium. During this early phase the added load of dietary electrolyte in the form of potassium chloride was a severe physiologic stress and two of the fifteen rats in this group died during this second month of the experiment. The remaining thirteen animals of this group adjusted to the diet and at 10 and 12 weeks the blood pressures were equal in the high Na group and high Na + K group. At 14 weeks the blood pressure was slightly higher in the high Na group than in the high Na + K while at 17 weeks the difference was even greater and at this time statistically significant ($p < 0.001$). At 19 and 27 weeks the blood pressures of the high Na group continued to climb and were significantly higher than the average value for the high Na + K group (at 19 weeks $p < 0.01$; at 27 weeks $p < 0.001$).

Exchangeable sodium in the control, high Na, and high Na + K was essentially equal when measured after 11 and 22 weeks on the experimental diets. At the twenty-seventh week, however, the rats fed the high sodium diet had significantly more $(NA)_E$ than those fed the same high sodium level with added potassium ($p < 0.001$). The high Na group also showed a significant elevation of $(Na)_E$ over the control group ($p < 0.03$). The rats fed high sodium with added potassium had less $(Na)_E$ than the control rats in spite of their very high intake of sodium chloride.

Total Body and Tissue Sodium: After the third measurement of exchangeable sodium the rats were killed and the carcass sodium or total body sodium $[(Na)_T]$ measured. In Table II it will be seen that the three groups of animals showed differences both in exchangeable and total body sodium. The high Na rats had more body sodium than did the controls or those fed high Na + K diets. The average percentage of carcass fat in the three groups is also shown since these values were used to calculate sodium content per unit of lean body weight. Sodium was measured in serum, muscle and heart from the three experimental groups (Table III). There were no significant differences in the serum sodium concentration in the three groups. Muscle sodium of the high sodium group was slightly higher than that of the controls and significantly ($p < 0.01$) higher than the group fed high Na + K. There was also somewhat

TABLE III
Serum and Tissue Sodium Content

Group	No. of Rats	Serum Na (mEq./L.)	Muscle		Heart	
			% H_2O ± S.E.M.	mEq. Na per 100 gm. Solids ± S.E.M.	% H_2O ±S.E.M.	mEq. Na per 100 gm. Solids ± S.E.M.
Control	10	142	74.9 ± 0.16	9.9 ± 0.24	77.5 ± 0.34	17.9 ± 0.59
High Na	9	145	75.7 ± 0.15	10.3 ± 0.33	78.4 ± 0.25	19.5 ± 0.90
High Na + K	10	144	75.4 ± 0.06	8.7 ± 0.28	78.1 ± 0.21	18.3 ± 0.80

more sodium in the hearts of the high Na group than either the control of high Na + K group. Thus the increases in sodium content of tissues were found in the animals that had increased exchangeable and total body sodium.

COMMENT

In these experiments rats fed 9.8 per cent dietary sodium chloride had increased blood pressure as well as increased exchangeable and total body sodium. Both blood pressure and exchangeable sodium were increased after 27 weeks on the diets. On the basis of available data it is impossible to state whether there exists a cause and effect relationship between the two observations. Animals fed diets containing 9.8 per cent sodium chloride with sufficient added potassium to restore the dietary ratio of Na:K to one, maintained significantly lower blood pressures and exchangeable body sodium.

The normal serum sodium levels in the rats which showed increased body sodium suggests that the increase resulted from expansion of the extracellular compartment.

SUMMARY

Rats fed 9.8 per cent sodium chloride and 6.1 per cent potassium chloride and 9.8 per cent sodium chloride and 0.6 per cent potassium chloride exhibited systolic blood pressure elevation after four weeks. At 8 weeks the Na + K group had significantly higher blood pressures. At 14 weeks the elevations were more marked in the high Na group and from 19 weeks these elevations were significantly higher. Exchangeable sodium, $(Na)_E$, in the controls, high Na and high Na + K groups was essentially equal at 11 and 22 weeks. At the twenty-seventh week, rats on the high Na diets had significantly more $(Na)_E$ than those fed the same high sodium with added potassium. The high Na group also showed a significant elevation of $(Na)_E$ over the control group. The rats fed Na + K had less $(Na)_E$ than the control rats. At sacrifice after 29 weeks measurements of total body sodium, $(Na)_T$, showed the same group differences. There was no significant difference in the serum sodium concentrations in the three groups. Increases in sodium content tissues were found in the rats with increased exchangeable and total body sodium.

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Resistance to Blood Flow through the Vascular Bed of the Dog Forelimb

Local Effects of Sodium, Potassium, Calcium, Magnesium, Acetate, Hypertonicity and Hypotonicity*

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ABOUT FOUR YEARS ago, we initiated a study of the direct effects of cations upon intact small and large blood vessels. We were particularly interested in their effects upon the arteriole because this structure provides the main variable resistance to blood flow. The test system was the vascular bed of the forelimb of a dog and various salts were infused into the brachial artery at rates which significantly raised the concentration of the cations in the leg without significantly affecting their concentrations in the body. All salts of sodium, potassium and magnesium decreased the resistance to blood flow through the vascular bed of the limb whereas all calcium salts increased the resistance to flow through this bed.[1,2] From these findings it was concluded that the local effect of raising the plasma concentration of sodium, potassium or magnesium was active arteriolar dilation and that of raising plasma calcium concentration was active arteriolar constriction. However, shortly after reporting these results, Read et al.[3] and Marshall and Shepard[4] observed a decrease in peripheral vascular resistance following intra-arterial administration of a hypertonic solution of glucose or urea. The solutions used in our experiments were also hypertonic; therefore, the observation of these investigators suggested that the changes attributed to sodium, potassium and magnesium might have resulted from increase of plasma tonicity. For this reason we have restudied the local actions of these ions, with particular attention to the problem of tonicity.

METHODS

Figure 1 presents our methods. A blood pump is interposed in the brachial artery so that the rate of blood flow through the forelimb can be held constant at 100 ml. per minute. Pressures are measured at four sites along the length of the bed. These sites include the brachial artery just distal to the pump, a small artery in the foot pad (0.5 mm.), a small vein on the dorsum of the paw (0.5 mm.) and the cephalic vein. Rate of flow is constant; therefore, any change in the pressure gradient from brachial artery to cephalic vein indicates a change in total resistance to blood flow. Similarly, changes of the gradients from the brachial artery to the small artery, small artery to small vein, and small vein to cephalic vein indicate changes in the resistance to flow through large arteries, small vessels and large veins, respectively. The gradient from small artery to small vein is of particular interest because most of this gradient results from resistance to flow through the arteriole. These methods have been described in detail previously.[5] Solutions were infused into the brachial artery at rates which varied plasma ion concentrations and/or tonicity in the limb without significantly affecting plasma ion concentrations and tonicity in the body.

RESULTS

Potassium and Calcium Salts: The plasma concentrations K^+ and Ca^{++} in the limb may be readily altered without changing plasma tonicity by infusion of *isotonic* solutions of K^+ and Ca^{++} salts. Figure 2A shows that infusion of isotonic KCl, 2 ml. per minute, in six dogs resulted in immediate decrease in arterial pressures, indicating fall of total vascular resistance due to fall of resistance in the small vessels. Isotonic $CaCl_2$, 2 ml. per minute, increased arterial pressures, indicating rise of total vascular resistance due to increase of resist-

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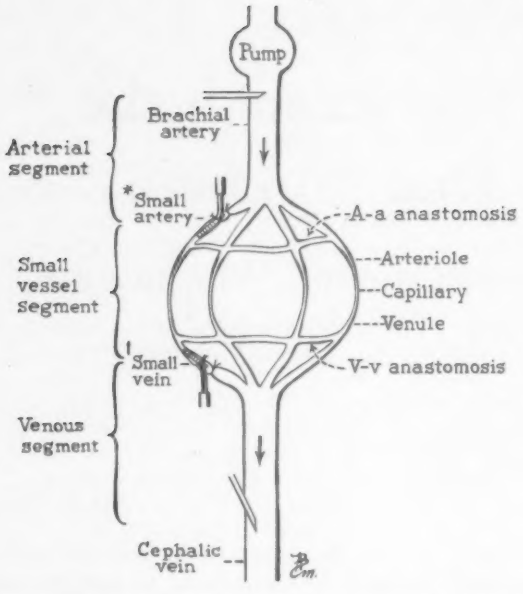


FIG. 1. Schematic drawing of the methods used for evaluating the effects of ions and tonicity upon the resistance to blood flow through the vascular bed of the dog forelimb. Large and small vessel pressures measured with the rate of blood flow in the brachial artery held constant at 100 ml. per minute. Solutions were infused into the brachial artery at rates which changed ion concentrations and/or tonicity in limb blood without significantly affecting ion concentrations or tonicity in the blood of the body. * Third superficial volar metacarpal artery. † Second superficial dorsal metacarpal vein.

ance in the small vessels. The action of $CaCl_2$ was prolonged. Isotonic NaCl, 2 ml. per minute, had no effect. Calculated increments in concentrations of plasma cations in the limb were 1.4 mEq. K^+ per L. during infusion of KCl, 3.8 mEq. Ca^{++} per L. during infusion of $CaCl_2$ and 0 mEq. Na^+ per L. during infusion of NaCl. The plasma Na^+ concentration is not readily altered by infusion of NaCl because the concentrations of Na^+ in plasma and in isotonic NaCl are about the same. On the other hand, infusion of an isotonic solution of KCl or $CaCl_2$ will elevate the plasma concentration of K^+ or Ca^+ because the concentration of the cation is much higher in the solution than in the plasma. The ability of isotonic KCl to cause a decrease in resistance of the small vessels was further substantiated by the higher infusion rate of 4 ml. per minute (Fig. 2B).

The specific effects of K^+ and Ca^{++} were further illustrated by infusions of 1 ml. per minute of equally hypertonic solutions of KCl, $CaCl_2$ and dextrose, each containing 2.78 Osm. per L. in three dogs (Fig. 2C). Infusion of hypertonic KCl resulted in three times the decrease of resistance in small vessels produced by equally hypertonic dextrose whereas equally hypertonic $CaCl_2$ definitely increased resistance.

Sodium Salts: The study of specific effects of Na^+ is much more difficult because plasma Na^+ concentration cannot be significantly increased without increasing plasma tonicity as well. The problem was approached by a comparison of several Na^+-containing compounds, NaCl, Na_2SO_4 and Na_2HPO_4. Due to differences in valence, aqueous solutions of these compounds all containing equal concentrations of Na^+, will differ osmotically, the NaCl solution having one and one third times the osmotic pressure of the other two. Also, aqueous solutions, all of equal osmotic pressure, will differ in concentrations of Na^+, the NaCl solution having only three-fourths the sodium concentration of the other two.

Two studies, differentially altering either plasma Na^+ concentration or tonicity in the limb, were made. In one study (Fig. 2D), hypertonic solutions were infused into ten dogs to provide identical amounts of Na^+ irrespective of tonicity. Solutions of NaCl, Na_2SO_4 and Na_2HPO_4 each containing 2 mEq. Na^+ per ml., were infused at 1 ml. per minute. Determination of the plasma Na^+ concentration in the cephalic venous blood in six dogs confirmed the calculated increment of 20 mEq. per L. for each infusion. Calculated increments in plasma tonicity in the limb were 40 mOsm. per L. for NaCl and 30 mOsm. per L. for Na_2SO_4 and Na_2HPO_4. Decreases in brachial arterial pressure were 21 mm. Hg for NaCl and 11 mm. Hg for both Na_2SO_4 and Na_2HPO_4. These changes roughly parallel tonicity and not Na^+ concentration.

In the second study, equally hypertonic solutions were infused irrespective of the amount of Na^+ supplied, and these were compared with an equally hypertonic solution of the nonelectrolyte, dextrose. Solutions of NaCl, Na_2SO_4 and dextrose, each containing 2.78 Osm. per L. were infused into six dogs at 2 ml. per min. (Fig. 3). Calculated increment in plasma tonicity in the limb was 56 mOsm. per L. for all infusions. Calculated increments in plasma Na^+ concentration in the limb were 28 mEq. per L. for NaCl, 37 mEq. per L. for Na_2SO_4, and 0 mEq. per L. for dextrose. Decreases in arterial pressures in the limb and, therefore, in the gradient across the small vessels

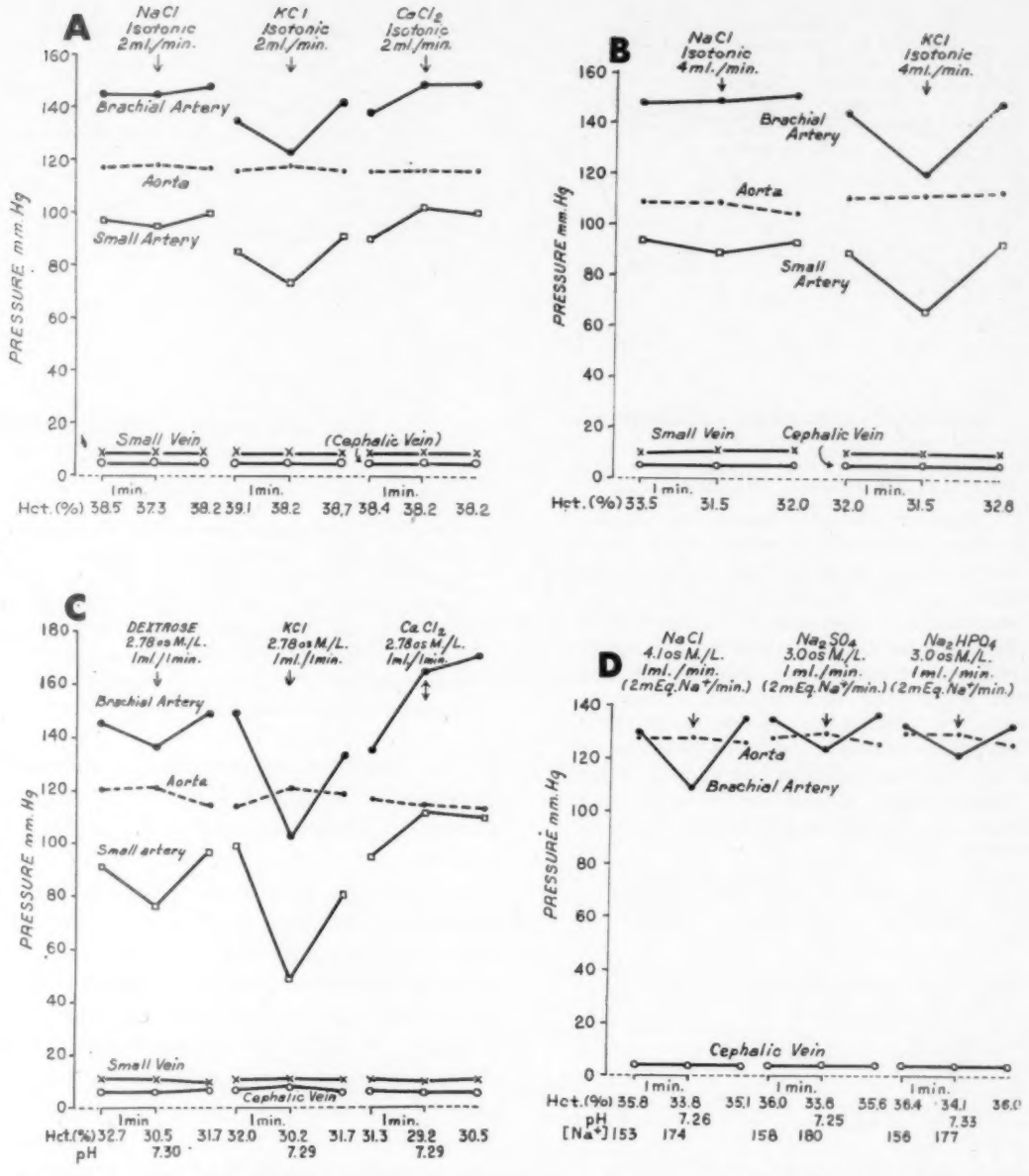


FIG. 2. A, effects of brachial arterial infusion of isotonic solutions of NaCl, KCl and $CaCl_2$ upon pressures in large and small blood vessels of the forelimb with rate of blood flow in the brachial artery held constant at 100 ml. per minute. Final pressures obtained about 5 minutes after stopping infusions. Values are averages of six animals. Hct. refers to hematocrit of cephalic venous blood (n = 5). B, effect of more rapid infusions of isotonic solutions of NaCl and KCl. See caption for Figures 1 and 2A. Values are averages of three animals. Hct. refers to hematocrit of cephalic venous blood (n = 2). C, effects upon pressures of equally hypertonic solutions of dextrose, KCl and $CaCl_2$ infused at equal rates. Values for pressures, hematocrit and pH are averages of three experiments. D, pressure changes caused by hypertonic solutions of sodium salts infused to produce equal increments in sodium concentration but different increments in total osmotic pressure. Averages of ten animals. Hct., pH and $[Na^+]$ refer to hematocrit (n = 10), pH (n = 10) and plasma sodium concentration (n = 6), respectively, of cephalic venous blood.

were similar for all infusions despite differing increments in Na^+ concentration.

Solutions containing 2.78 Osm. per L. of NaCl, Na_2SO_4 and dextrose were also infused at the higher rate of 3.6 ml. per minute in nine dogs (Fig. 4). Calculated increments in limb plasma tonicity were 100 mOsm. per L. for all infusions. Calculated increments in limb plasma Na^+ concentration were 50 mEq. per L. for NaCl, 65 mEq. per L. for Na_2SO_4 and 0 mEq. per L. for dextrose. Decreases in large and small arterial pressures and, therefore,

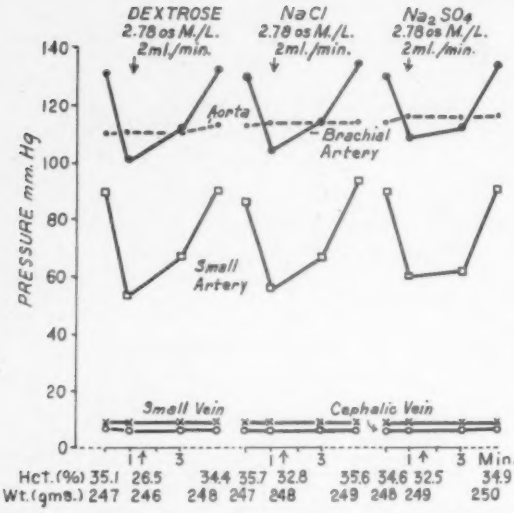


FIG. 3. Pressure changes caused by hypertonic solutions infused to produce equal increments in osmotic pressure but different increments in sodium concentration. Averages of six experiments. Hct. refers to hematocrit (n = 5) of cephalic venous blood. Wt. refers to weight of forelimb (n = 6). Weight was measured by placing the limb on a scale at table top level. Since the shoulder joint acted as a fulcrum, attention is given to direction of change of weight and not absolute values. Most limbs spontaneously gained weight with time because of the slightly dependent position in relation to the heart.

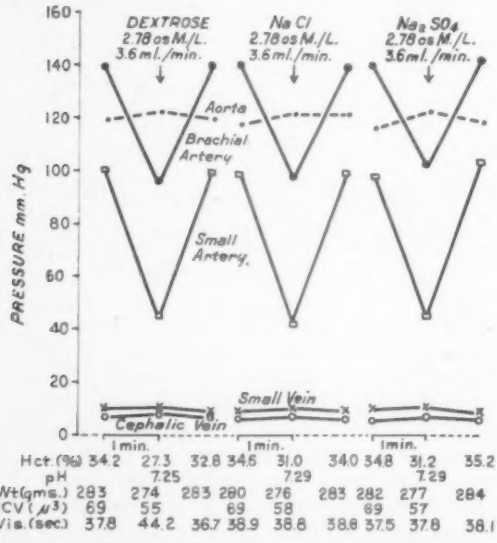


FIG. 4. Pressure changes produced by hypertonic solutions infused to produce equal increments of osmotic pressure but different increments in sodium concentration. Averages of nine experiments. Infusion rate more rapid than in experiment described in Figure 3. Hct., pH, Wt., MCV and Vis. refer to hematocrit (n = 9), pH (n = 8), limb weight (n = 2) mean corpuscular volume (n = 2) and viscosity (n = 4), respectively, of cephalic venous blood. Viscosity measured in a glass viscometer at 37°C. See legend for Figure 3 for explanation of weight.

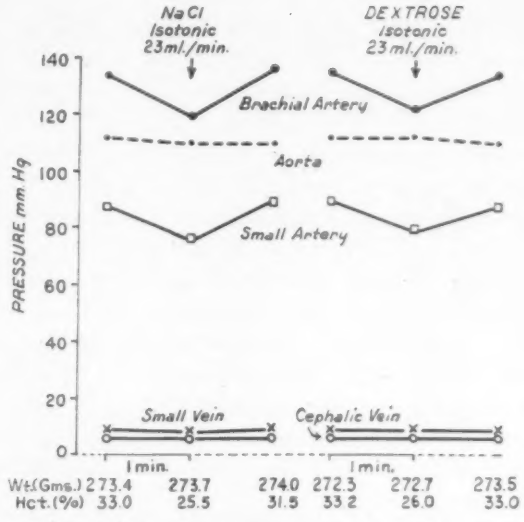


FIG. 5. Effect upon pressures of decreasing limb plasma Na^+ concentration without altering tonicity. Isotonic solutions infused proximal to the pump in order that flow rate remained at 100 ml. per minute. Averages of six experiments. Wt. and Hct. refer to weight (n = 6) and hematocrit (n = 3), respectively, of cephalic venous blood.

in the gradient across the small vessels were practically identical for all infusions. These changes parallel tonicity and not Na^+ concentration.

An attempt was made to study the effect of decreasing plasma Na^+ concentration in the limb without altering tonicity. In six dogs, an isotonic solution of dextrose was infused at a rapid rate, 23 ml. per minute, and an isotonic solution of NaCl served as a control (Fig. 5). These infusions were made into the proximal side of the pump in order to avoid changing the rate of flow to the limb. Determination of the venous plasma Na^+ concentration in the limb in one animal confirmed the calculated decrement of plasma Na^+ concentration in the limb of 35 mEq. per L. during infusion of isotonic dextrose and of 0 mEq. per L. during infusion of isotonic NaCl. The decrease in arterial pressures and, therefore, in the gradient across the small vessels during infusion of isotonic dextrose was equal to that during infusion of isotonic NaCl, again providing no evidence for an effect of sodium. As will be demonstrated, the decrease in resistance resulted, at least in part, from a decrease in viscosity of the blood.

Magnesium and Acetate Salts: Isotonic solutions of $MgCl_2$, $MgSO_4$, $Mg(Ac)_2$ and NaAc were infused into ten dogs. Mg^{++} was delivered at 13 mg. per min. in the case of the

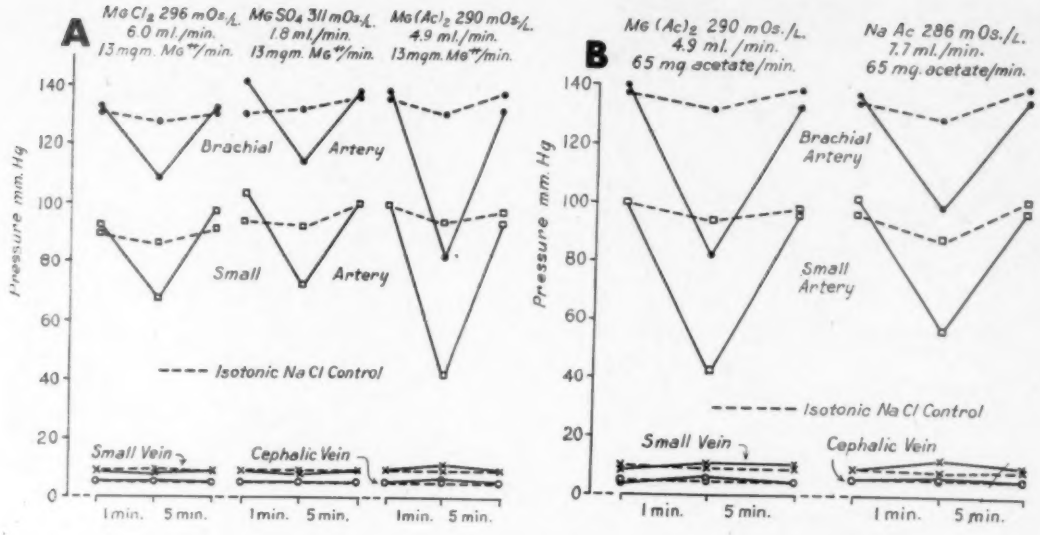


FIG. 6. A, effects on pressures of isotonic solutions of $MgCl_2$, $MgSO_4$ and $Mg(Ac)_2$ infused to deliver 13 mg. Mg^{++} per minute. Each infusion of a Mg^{++} salt was preceded by infusion of isotonic NaCl at the same volume rate. Averages of ten experiments. B, effects on pressures of isotonic solutions of $Mg(Ac)_2$ and NaAc infused to deliver 65 mg. Ac^- per minute. Each infusion of an Ac^- salt was preceded by infusion of isotonic NaCl at the same volume rate. Same ten animals as depicted in Figure 6A.

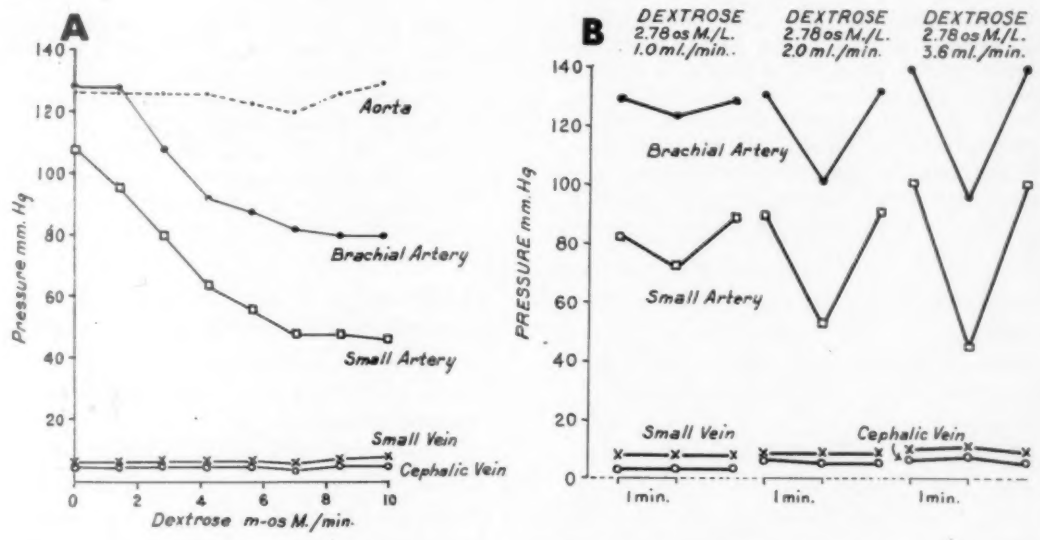


FIG. 7. A, effect on pressures of a hypertonic solution of dextrose (2.78 Osm. per L.) in one animal. Pressures are plotted as a function of the infusion rate of dextrose in mOsm. per minute. Pressures were recorded as soon as they became steady. Entire sequence completed in 15 minutes. B, effects on pressures of infusion of a hypertonic solution of dextrose into the brachial artery at 1, 2, and 3.6 ml. per minute. Averages of ten, six and nine experiments, respectively.

Mg^{++} salts and acetate at 65 mg. per min. in the case of the Ac^- salts. An isotonic solution of NaCl, infused at the same volume rates as the salts of Mg^{++} and Ac^-, served as a control. The pressure gradient from brachial artery to cephalic vein decreased 27 mm. Hg during infusion of $MgSO_4$ and $MgCl_2$, and 58 mm. Hg during infusion of $Mg(Ac)_2$ (Fig. 6A). Infusion of NaCl at the same volume rates produced decrements of 0, 4 and 5 mm. Hg, respectively. In the same animals NaAc and its NaCl control (Fig. 6B) produced decrements of 42 and 6 mm. Hg, respectively. NaAc also produced a slight increment in the gradient from small to cephalic vein. In several animals, the pH of brachial arterial and cephalic venous blood was measured before, during and after infusion of the salts. The values did not change

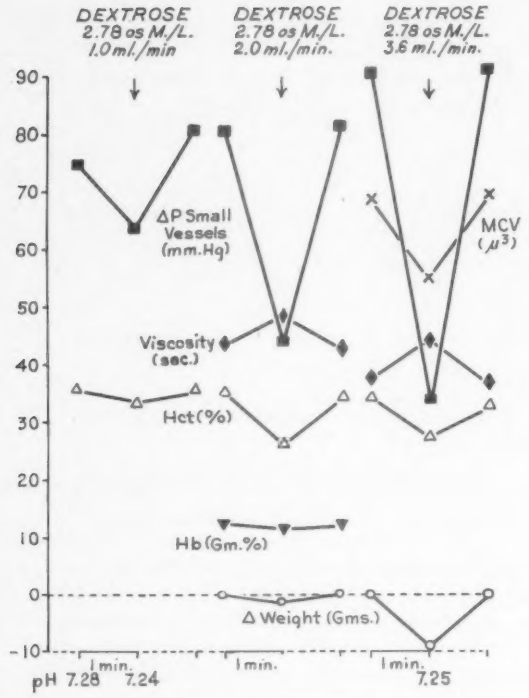


FIG. 8. Additional data from the experiments depicted in Figure 7B. ΔP Small Vessels refers to the pressure gradient from small artery to small vein (n's = 10, 6, 9), ΔWeight to change in forelimb weight from the precontrol value (n's = 6, 2), and viscosity, Hct., Hb., MVC and pH to viscosity (n's = 1, 4), hematocrit (n's = 10, 5, 9), hemoglobin concentration (n = 2), mean corpuscular volume (n = 2) and pH (n's = 10, 8), respectively, of cephalic venous blood.

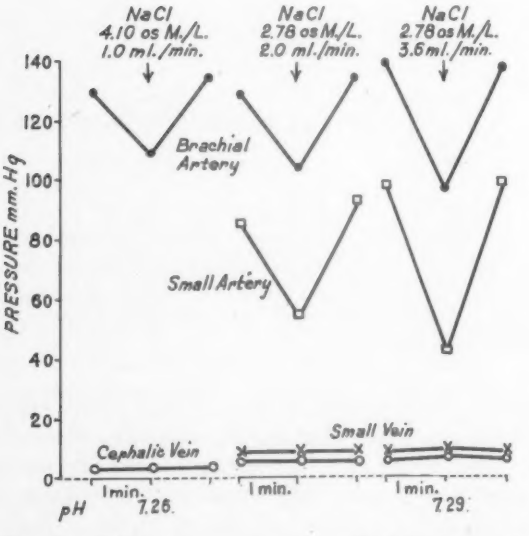


FIG. 9. Effects on pressures of administration of hypertonic solutions of NaCl at three rates. Averages of ten, six and nine experiments, respectively. pH refers to pH (n's = 10, 8) of cephalic venous blood.

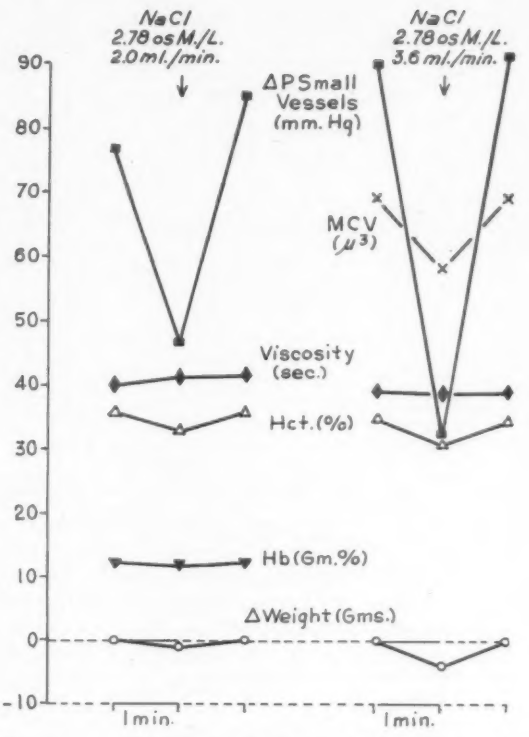


FIG. 10. Additional data from experiments described by Figure 9. ΔP Small Vessels refers to pressure gradient from small artery to small vein (n's = 6, 9), ΔWeight to change in forelimb weight from pre-control value (n's = 6, 2), and Viscosity, Hct., Hb. and MCV to viscosity (n's = 1, 4), hematocrit (n's = 5, 9), hemoglobin concentration (n = 2) and mean corpuscular volume (n = 2), respectively, of cephalic venous blood.

significantly. These findings suggest that the local effect of an excess of both Mg^{++} and Ac^{-} is active arteriolar dilation. Ac^{-} is the first anion encountered to have significant action in this preparation.

Changes in Plasma Tonicity: We next directed our attention to the mechanism of the resistance changes which result from change of plasma tonicity. Additional measurements were made of cephalic venous blood before, during and after infusion of hypertonic and hypotonic solutions. These measurements included viscosity, hematocrit reading, hemoglobin concentration, mean corpuscular volume and blood pH. Limb weight was also measured by placing the limb on a scale.

Figure 7A presents pressures as a function of the infusion rate of a 2.78 Osm. per L. solution of dextrose into one animal. Figure 7B presents average pressure before, during and after infusion of a hypertonic solution of dextrose (2.78 Osm. per L.) at 1, 2 and 3.6 ml. per minute, respectively. Brachial and small ar-

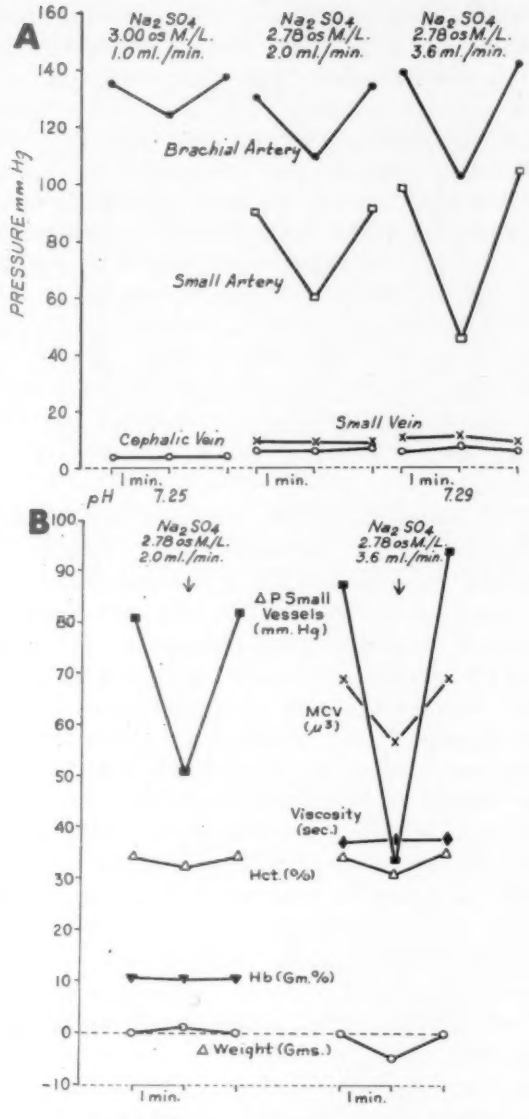


FIG. 11. A, effects on pressures of administration of hypertonic solutions of Na_2SO_4 at three rates. Averages of ten, six and nine experiments, respectively. pH refers to pH (n's = 10, 8) of cephalic venous blood. B, additional data from experiments described in A. ΔP Small Vessels refers to pressure gradient from small artery to small vein (n's = 6, 9), Δ Weight to change in forelimb weight from the pre-control value (n's = 6, 2), and Viscosity, Hct., Hb., and MCV to viscosity (n = 4), hematocrit (n's = 5, 9), hemoglobin concentration (n = 2) and mean corpuscular volume (n = 2), respectively, of cephalic venous blood.

terial pressures decreased almost equally and the degree of fall increased as a function of the rate of infusion. Figure 8 presents additional data from the same experiment. In association with the fall in the pressure gradient from small artery to small vein were decreases in mean

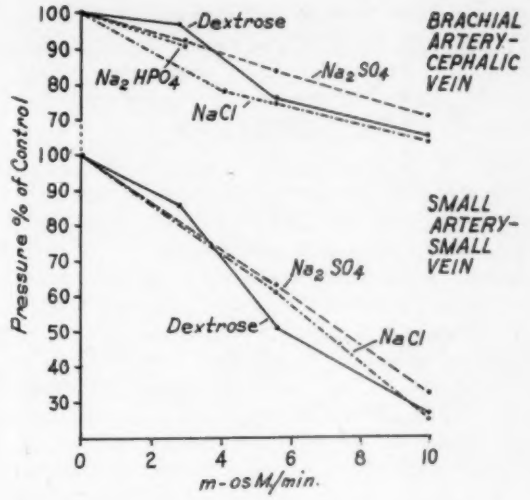


FIG. 12. Comparison of effects of hypertonic solutions of dextrose, NaCl, Na_2SO_4 and Na_2HPO_4 upon total and small vessel pressure gradients. Pressure gradients, in per cent of pre-control value, are plotted against the infusion rate in mOsm. per minute. Data obtained from experiments described by Figures 7B, 9 and 11.

corpuscular volume, hematocrit and limb weight. There was also a very small fall of hemoglobin concentration. Blood viscosity increased.

Hypertonic solutions of NaCl and Na_2SO_4 were studied in a similar manner (Figs. 9, 10, 11). The findings were the same except that these solutions did not affect blood viscosity.

Figure 12 compares the effect of these hypertonic solutions upon average pressure gradients from brachial artery to cephalic vein and from small artery to small vein; that is, the total gradient and the small vessel gradient. These gradients, in per cent of control values, are plotted against the infusion rate in mOsm. per minute. The slopes of the lines are not greatly different, suggesting that the mode of action of these agents is the same. These data also provide further evidence that the sodium does not have a specific action of its own. Further, they suggest that the chloride, sulfate and biphosphate ions do not have measurable specific activity.

Hypertonic urea also decreased pressures in brachial and small arteries without affecting venous pressures in this preparation.

In other experiments, tonicity was lowered by rapidly infusing hypotonic solutions and the responses were compared with those due to equally rapid infusions of isotonic solutions (Fig. 13). The solutions were administered proximal to the pump so that flow rate through

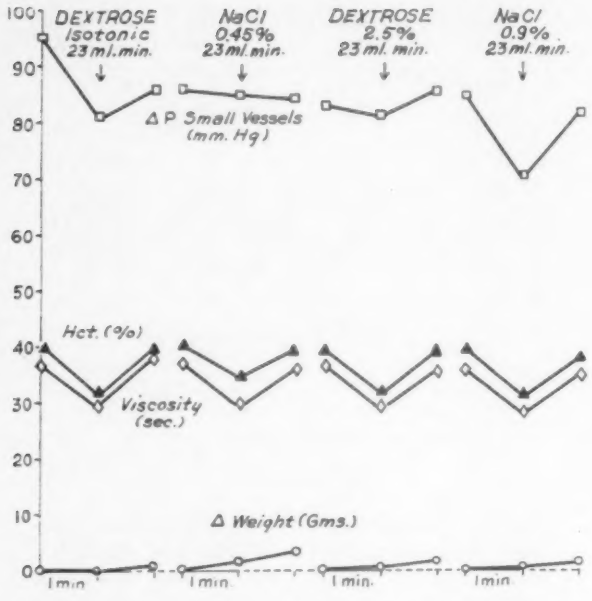


FIG. 13. Effects of lowering tonicity by rapid infusion of hypotonic solutions and comparison with equally rapid infusion of isotonic solutions. Infusions administered proximal to pump in order that flow rate remained at 100 ml. per minute. Δ P Small Vessels refers to pressure gradient from small artery to small vein (n = 11), Δ Weight to change in limb weight (n = 7), Hct. to hematocrit of cephalic venous blood (n = 7), and Viscosity to viscosity of cephalic venous blood (n = 7).

the limb did not change. The pressure gradient of the small vessels decreased during infusion of isotonic NaCl or isotonic dextrose at 23 ml. per minute but did not change during infusion of hypotonic NaCl or dextrose at the same rate. That there must have been constriction of small vessels during infusion of the hypotonic solutions is indicated by an unchanging resistance, despite fall of blood viscosity. In contrast, vessel calibers probably did not change during infusion of isotonic solutions. The decrease of viscosity is probably adequate to explain the decrease of resistance.

COMMENTS

These studies show that acute local elevation of the plasma concentration of K^+ and of Mg^{++} within physiologic ranges by infusion of isotonic salts substantially decreases the resistance of the small vessels in the limb. Acute local elevation of the Ca^{++} concentration by the same method increases resistance of the small vessels. These findings suggest that K^+ and Mg^{++} actively dilate arterioles and Ca^{++} actively constricts arterioles, and that these effects are independent of changes in tonicity. On the other hand, acute increase or decrease of the sodium concentration has little effect upon the resistance of small vessels other than that attributable to changes in plasma tonicity. This suggests that the sodium ion probably has little specific action upon the contractile mechanism of arteriolar smooth muscle. Elevation of the concentration of acetate by infusion of isotonic acetate salts decreases resistance to blood flow through small vessels. Hence, the local action of acetate excess is active arteriolar dilation. This is the first anion encountered to have significant action in this preparation. Its ability to simultaneously dilate arterioles and constrict veins suggests a role in water storage in tissues.

The mechanism of action of changes in tonicity is not entirely clear. Increase of tonicity by infusion of a hypertonic solution of dextrose, urea or of a sodium salt results in decrease of small vessel resistance. It is clear that the decrease in resistance results from dilation because viscosity either increases or does not change. This dilation is associated with movement of water out of the limb because the weight of the limb decreases. The water comes at least in part from within cells because the decrease in weight is associated with a fall in mean corpuscular volume. Thus, the dilation could be a passive phenomenon due to dehydration of vessel walls. One cannot, however, eliminate active dilation because withdrawal of water from cells undoubtedly concentrates the ions within the cells and many of these ions can produce active change of caliber. The hypotonic solutions studied decrease calibers. This constriction may be passive, due to overhydration of the vessel wall or active, due to changes in concentrations of intracellular ions.

Returning to K^+, Ca^{++}, Mg^{++} and Ac^-, it should be emphasized that the changes described are the result of local actions. In some instances, when concentrations are raised generally within an animal, a remote action may modify or obscure the local action. For example, the local dilatory action of potassium may not become manifest following intravenous administration because of discharge of catecholamines from the adrenal medulla. It should also be noted that the local actions of cations upon blood vessels and heart are similar. Calcium stimulates both structures whereas potassium and magnesium depress both structures. It is difficult to demonstrate an action of sodium upon the heart. It is also difficult to

demonstrate that this ion has a specific action upon blood vessels.

Summary

Evidence is presented which indicates that, in the foreleg of the dog, the local effect of acute slight elevation in the blood concentration of potassium, magnesium or acetate is active arteriolar dilation whereas the local effect of slight elevation of calcium concentration is active arteriolar constriction. Increase or decrease in the concentration of sodium seems to have little effect independent of that due to change of blood tonicity. Increase in blood tonicity produces dilation whereas decrease in tonicity produces constriction. These caliber changes may be passive, due to dehydration or overhydration of the arteriolar wall, or active, due to increase or decrease in the concentration of ions within the smooth muscle cell. These findings may be relevant to the problem of arterial hypertension.

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Effect of Hypertension and Sodium Chloride on Vascular Reactivity in Vitro*

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ONE RECENT concept of the etiologic factors in hypertension especially attractive to me is that one relating hypertension to enhanced vascular reactivity. It seemed to me that essential hypertension might be a result of the transmission of a gene or genes responsible for the development of some alteration in a component of the vascular walls, such as an enzyme or contractile protein of the smooth muscle, resulting in an enhanced reactivity of these walls. In secondary and experimental hypertension, although hereditary transmission of the altered characteristic would not be responsible, the same vascular change might occur as a result of environmental influences within the body. If this were true, a clue to the nature of the similar "defect" in the vascular walls of the animal with essential hypertension might result from study of animals with experimental hypertension.

Having an interest in the contractile proteins of muscle, I became interested in the possibility of comparing the reactivity of the contractile protein actomyosin, obtained from the vascular walls of the normotensive animal, with that obtained from the vessels of the hypertensive animal, especially during the initial period of the development of experimental hypertension. Fortunately, I first investigated whether any reactivity greater than normal could be established in the *total* vascular wall of the experimental hypertensive animal. To eliminate circulatory, nervous and similar influences present in the intact animal, the behavior of vascular strips *in vitro* was studied. It would have been more pertinent to study the reactivity of arterioles rather than of arterial strips, but because of the obvious technical difficulties and because I planned to extract the actomyosin from the vessel walls later, I chose to extrapolate to aortic strips. Such strips had already been extensively employed as models in the study of the physiology and pharmacology of vascular smooth muscle.

METHODS

To compare precisely the reactivities of vascular segments from normotensive and from hypertensive animals, it was necessary to prepare strips from control and experimental animals as closely alike as possible. It was not possible to do this using spirally cut strips, but was possible using an adaptation of the technic of Vick, Ederstrom and Vergeer.[3] According to this method, a cylindrical strip of aorta is removed from an animal, freed of extraneous fat and connective tissue, and slit open lengthwise. Incomplete transverse cuts are then made on alternate sides of the strip to obtain a saw-tooth shaped segment (Fig. 1). By pinning a strip from a hypertensive rat and one from a normotensive rat together on a cork, and using a razor blade in cleaver fashion, both strips could be cut simultaneously so that they would be exactly alike in length, width and transverse cuts, and could differ only in thickness.

When these strips were subjected to stretch, the elongation permitted the circular muscle layers to exhibit an increased vertical component of tension when stimulated to contract. Each pair of identically-cut strips was placed in a bath containing Krebs-Ringer bicarbonate buffer solution, subjected to an initial tension of 2 gm., and allowed to relax for 2.5 to 3 hours from the trauma of cutting, during which time the strips developed maximum sensitivity to the added drugs. After readjustment to 2 gm. of tension, isometric contractions, occurring as a result of the addition of l-epinephrine or l-norepinephrine (final concentrations $1:10^9$–$1:10^5$) were recorded on a Grass polygraph. The catecholamines were used as stimulating agents to mimic the physiologic stimuli. Contraction of each pair of strips was induced two or three times, allowing suitable periods of relaxation between contractions. Following the contractions the strips were washed, weighed, the "muscle" com-

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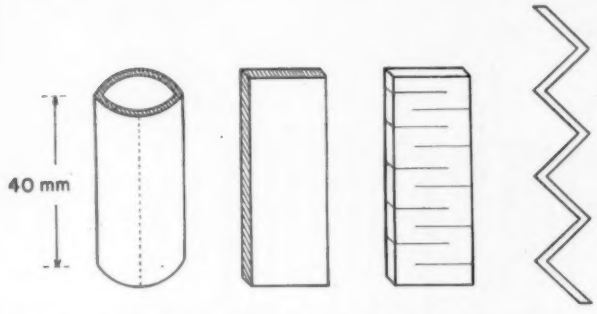


FIG. 1. Method of preparing aortic strips (according to Vick, Ederstrom and Vergeer[3]). FROM: MALLOV, S. *Circulation Res.*, 7: 196, 1959.[1]

ponents extracted with NaOH and the "muscle" (alkali-soluble) nitrogen of the extracts determined.[4]

Male albino rats were used as the experimental animals; some were rendered hypertensive by one of two procedures as follows: (1) the weekly intramuscular injection of 5 mg. desoxycorticosterone trimethylacetate (DCA) and the substitution of 1 per cent NaCl for drinking water; (2) the tying of figure-of-eight ligatures around the left kidneys, and the removal of the right kidneys 1 to 2 weeks later. Blood pressures were determined by means of the microphonic manometer method of Friedman and Freed on nonsedated animals. Rats with systolic pressures not exceeding 130 mm. Hg were considered normotensive; those with pressures of 150 and higher were considered hypertensive. Pairs of rats, composed of one control and one hypertensive animal, were killed 14 to 105 days following the initiation of DCA administration, or following the second renal operation.

RESULTS

Aortic Hypertrophy: Both DCA and renal hypertension were associated with aortic hypertrophy (Table 1). Not only did the strips of aorta from hypertensive rats tend to weigh more than did the corresponding strips from the normotensive animals, but also the former contained significantly greater quantities of smooth muscle as indicated by the values of muscle nitrogen per unit of tissue weight.

Vascular Reactivity to Catecholamines: To my

TABLE 1

Isometric Contractions, Tissue Weights and Muscle Nitrogen Contents of Aortic Strips from Hypertensive and Normotensive Rats

Measurement	DCA-Salt Hypertension	Renal Hypertension
Blood pressure		
Hypertensive (mm. Hg)	199 ± 5.0* (28)†	162 ± 2.3 (27)
Control	124 ± 1.2 (28)	126 ± 0.6 (27)
Difference in maximum tension exerted by aortic strips (%)		
In response to l-epinephrine‡	2−43. ± 4.98 (28)	−18.4 ± 6.96 (27)
In response to levarterenol	−37.2 ± 7.16 (16)	−18.4 ± 8.89 (17)
Difference in wet tissue weight of aortic strips§	+21.1 ± 3.61 (26)	+23.1 ± 5.02 (27)
Muscle nitrogen (μg.) per mg. aortic tissue (wet weight)		
Hypertensive rats	14.83 ± 0.463 (26)	14.87 ± 0.414‖ (27)
Control rats	11.58 ± 0.434¶ (26)	13.40 ± 0.422 (27)

FROM: MALLOV, S. *Circulation Res.*, 7: 196, 1959.[1]

* All figures are given as mean ± standard error of the mean.

† Figures in parentheses represent number of rats or of aortic strips.

‡ Maximum tension expressed as mg. tension per mg. muscle nitrogen. Per cent difference for each pair of strips calculated as H-C/C × 100; H and C are maximum tension exerted by hypertensive and control strip, respectively.

§ Per cent differences for each pair of strips calculated as H-C/C × 100; H and C are mg. wet tissue weight of hypertensive and control strip, respectively.

¶ Difference between values for hypertensive and control strips statistically significant ($P < 0.01$).

‖ Difference between values for hypertensive and control strips statistically significant ($P < 0.02$).

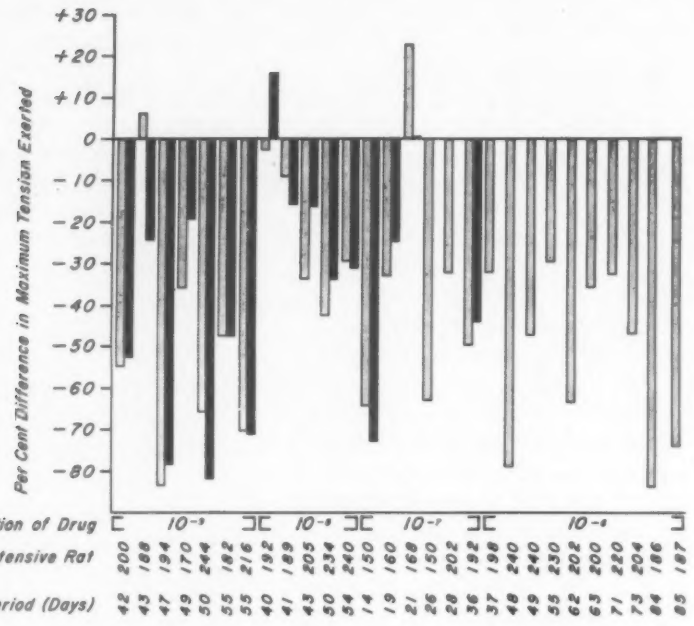


FIG. 2. DCA-salt hypertension. Per cent difference in maximum tension exerted between each aortic strip from a DCA-salt hypertensive rat and its normotensive control, in response to l-epinephrine (shaded bars) or levarterenol (black bars). Tension is expressed as mg. tension per mg. muscle nitrogen. FROM: MALLOV, S. *Circulation Res.*, 7: 196, 1959.[1]

surprise, it was found that instead of the expected increase in reactivity of hypertensive rat aortic strips, the latter were less reactive in response to epinephrine and norepinephrine than were the strips from the normotensive control rats. Thus, of forty-four strips obtained from DCA-salt hypertensive rats, forty responded to various doses of the catecholamines with smaller contractile tensions than did the corresponding strips from the normotensive controls. Of all forty-four pairs of strips, the strips from hypertensive rats manifested, on an average, 40 per cent smaller contractions than the strips from normotensive rats. In the case of the renal hypertensive rats, of forty-four pairs of strips, thirty-three strips from hypertensive animals responded with smaller contractions than did the corresponding strips from normotensive rats, the mean difference in tension between hypertensive and normotensive strips for all forty-four pairs being 18.4 per cent (Figs. 2 and 3).

Thus, there was no evidence for increased reactivity of vascular walls associated with the development or existence of experimental hypertension. I believe that the generally decreased reactivity exhibited by the strips from hypertensive rats was a consequence of the hypertension itself. With the rapidity of the development of the hypertension in these animals, there must be a rapid deterioration of the vascular walls. Thus, the tendency to reduced reactivity was much more marked in the aortas of the DCA-salt hypertensive rats, whose blood pressures, in general, were considerably higher than those of the renal hypertensive animals. In a few instances in which the blood pressures were especially high, hypertrophy, tortuosity and sclerosis of the aorta were easily discernible to the naked eye. Therefore, it appears that one of the difficulties in using experimental hypertensive animals in experiments such as described may be the confounding of etiologic factors with the sequelae of hypertension, as a result of the rapidity of development and the severity of the hypertension.

SODIUM CONCENTRATION AND AORTIC CONTRACTILITY

Vick, Ederstrom and Vergeer[3] reported increased reactivity of aortic strips obtained from rats on a high salt diet; therefore, I was especially interested in the failure of DCA-salt induced hypertension to cause increased vascular reactivity. Salt or sodium ion has long been implicated in the etiology of experimental and essential hypertension. Increased concentrations of sodium and water have been reported

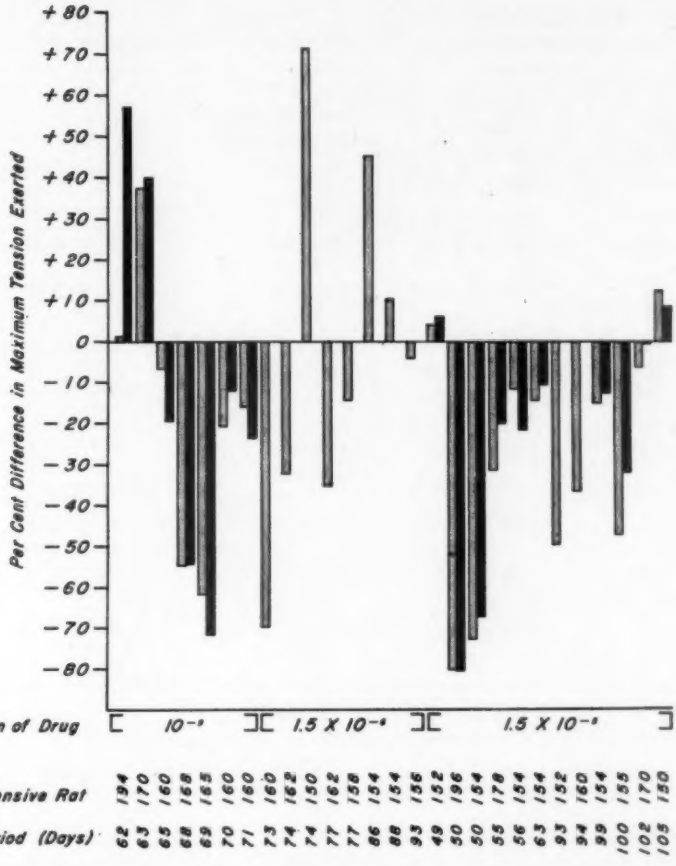


FIG. 3. Renal hypertension. Per cent difference in maximum tension exerted between each aortic strip from a renal hypertensive rat and its normotensive control, in response to l-epinephrine (shaded bars) or levarterenol (black bars). Tension is expressed as mg. tension per mg. muscle nitrogen. FROM: MALLOV, S. *Am. J. Physiol.*, 198: 1019, 1960.[2]

to be present in the arterial walls of animals with experimental hypertension. It has been suggested that excessive intracellular sodium may increase the sensitivity of vascular smooth muscle as a result of an effect on the contractile protein system or on the membrane potential. *In vitro* studies of the effect of sodium on vascular reactivity have had somewhat conflicting results.[5–7] Therefore it was thought of interest to assay the effects of altered sodium concentrations on the reactivities of the aortic strip preparations. Since strips from normotensive and hypertensive rats showed different reactivities, I wondered whether the responses to stimulation in the presence of altered sodium concentrations would also be different. If they were different one could not extrapolate results obtained with vessels from normotensive animals to those from hypertensive ones.

Therefore, aortic strips from rats made hypertensive by DCA and 1 per cent saline administration, were prepared as previously described, and the contraction of each strip in the presence of a deficiency or of an excess of sodium chloride was compared with its own contraction in the presence of normal sodium concentration. L-Epinephrine bitartrate in a final concentration of $1:10^9$ was employed to induce contraction. This concentration was much smaller than that required to induce maximum contraction. After the initial contraction in normal Krebs-Ringer bicarbonate solution, the bath fluid was washed out and replaced by the same solution with an altered concentration of sodium. Each strip was then allowed 1 hour to come into equilibrium with the new solution before being induced to contract by a second addition of epinephrine. During this time, changes in tension were recorded. In some instances, following washout, a third contraction was induced in normal Krebs-Ringer bicarbonate solution. Since it has been suggested that the intracellular sodium ion concentration, which may be affected by the extracellular situation, is the determining factor in controlling membrane potentials and thereby controlling the contractility of smooth muscle, it was thought that

TABLE II
Isometric Contractions of Aortic Strips from Normotensive and Hypertensive Rats

Rat Type	No. Rats	Systolic Blood Pressure (mm. Hg)	Bath Medium for Contraction 2 or 3	Percentage Change*	
				Contraction 2	Contraction 3
N	20	123 ± 1.2	Normal KRB	+ 9.4 ± 7.22	− 3.6 ± 8.09
H	16	191 + 4.6	Normal KRB	+ 6.5 ± 3.47	+11.0 ± 5.23
N	53	122 ± 0.9	High Na	+73.5 ± 15.64	...
H	36	191 ± 3.8	High Na	−28.7 ± 7.63	...
N	22	122 ± 1.0	Low Na	−19.5 ± 5.76	...
H	20	191 ± 5.8	Low Na	−19.6 ± 5.501	...
N	14	125 ± 1.3	Normal KRB + Sucrose	+76.7 ± 13.16	...
H	14	188 ± 4.6	Normal KRB + Sucrose	−32.3 ± 5.84	...
N	18	120 ± 2.0	Low Na + Sucrose	+ 1.3 ± 4.14	...
H	17	188 ± 4.2	Low Na + Sucrose	±16.8 ± 9.34	...

FROM: MALLOV, S. *Am. J. Physiol.*, 198: 1019, 1960.[2]
Values are means ± S.E. N = normotensive; H = hypertensive; KRB = Krebs-Ringer bicarbonate solution.
* Calculated as (second or third contraction − first contraction) × 100/(first contraction).

by allowing the strips to reach equilibrium with solutions of altered sodium concentration prior to inducing contraction, instead of causing contraction immediately following change of bath fluid, one would more closely approach the *in vivo* situation.

Increased Sodium Concentration: The results obtained are shown in Table II. When the sodium ion concentration was elevated from 143.3 to 180.3 mEq. per L., the strips from the normotensive rats showed an increased contractility, and the strips from the hypertensive rats demonstrated decreased contractility. Despite considerable variation from strip to strip, the differences between these changes and those occurring with time, in normal solution, were statistically significant. It was also observed that during the "rest period" of 1 hour, when the strips remained in the high sodium solution prior to the second addition of epinephrine, the strips taken from the hypertensive animals gradually increased in tension, while no significant changes in tension were noted in the strips taken from normotensive control rats (Fig. 4).

Decreased Sodium Concentration: When the sodium concentration of the medium was reduced to 106.3 mEq. per L. an equal reduction of reactivity occurred in aortic strips from both normotensive and hypertensive rats, and no significant change in tension was undergone by any of these strips while remaining in the low sodium medium for 1 hour, prior to the induction of contraction. Again, the reduction in contraction resulting from exposure to the medium low in sodium was statistically significant.

Tonicity of Sodium Solutions: To evaluate the contribution of altered tonicity to the contractility changes in Krebs-Ringer bicarbonate solution, sucrose was first substituted in isoosmolar quantity for the excess of sodium chloride of the high sodium concentration solution. Sucrose produced the same changes in reactivity as did the sodium in high concentrations. During the 1 hour period of equilibration in the hypertonic sucrose solution, prior to the second contraction, the strips from the hypertensive rats manifested gradual increases in tension but those from the normotensive rats did not. Strips from both normotensive and hypertensive rats returned to normal contractility when sucrose, sufficient to restore the tonicity to normal limits, was added to the Krebs-Ringer bicarbonate medium low in sodium. The strips reacted as if they were in Krebs-Ringer solution of normal sodium concentration, and there were no significant changes in tension in any of the strips during the equilibration period prior to the second contraction. These experi-

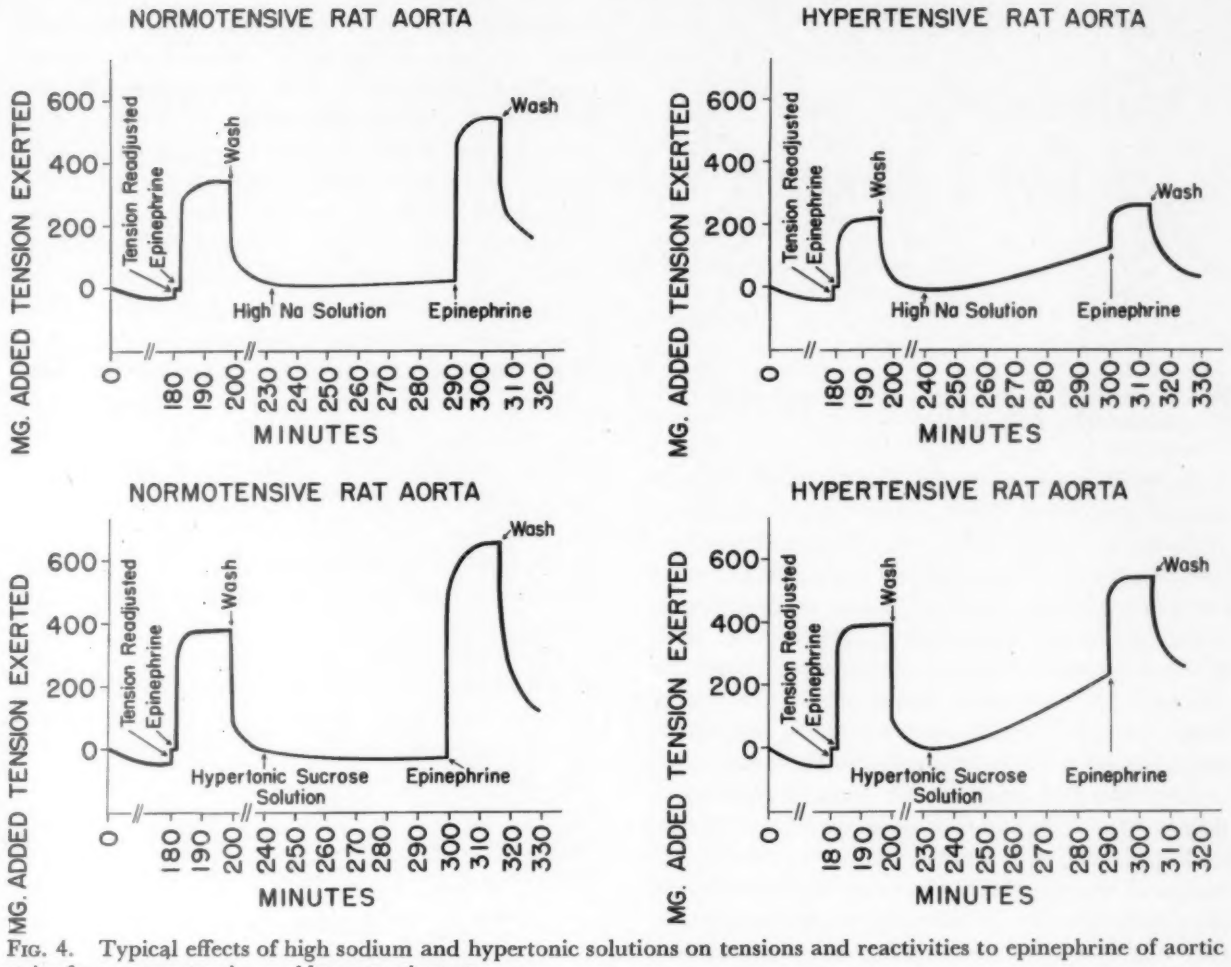


FIG. 4. Typical effects of high sodium and hypertonic solutions on tensions and reactivities to epinephrine of aortic strips from normotensive and hypertensive rats.

ments with sucrose indicate that if one considers sucrose to be inert, then the changes in reactivity of the strips in solutions of altered sodium concentration might not be due to the changes in sodium concentration *per se*, but rather to changes in tonicity of solution.

The increases in tension manifested by the strips from hypertensive rats when placed in hypertonic media alone prior to the addition of epinephrine ranged from 50 to 90 per cent of the increases in tension produced by addition of epinephrine to the same strips when they were maintained in isotonic solution. Therefore, it appears that the reduced reactivities of the strips from hypertensive rats in hypertonic solution manifested after the addition of epinephrine may have been a consequence of the strips being already partly in the contracted state at the time epinephrine was added.

In another experiment an attempt was made to ascertain whether the difference in reactivity between aortic strips from hypertensive and normotensive rats in high sodium medium could be ascribed to the effects of DCA and 1 per cent saline *per se*, or was a result of the hypertension that ultimately developed. A number of rats were given injections of DCA and 1 per cent saline to drink for a period of 1 week. At the end of this time they did not show any hypertension, and the aortic strips reacted similarly in the presence of high concentrations of sodium to the strips from the untreated control rats.

COMMENT

What can we conclude from these experiments? They do not indicate the increased reactivity of vessel walls of experimental hypertensive animals that I was looking for. I believe they do show that as a *consequence* of hypertension, arterial walls become not only structurally but also functionally altered, and that this functional alteration includes a *decreased* reactivity to catecholamines and a changed contractile behavior in the presence of high sodium concentrations and hypertonic solutions. Other investigators have reported such functional

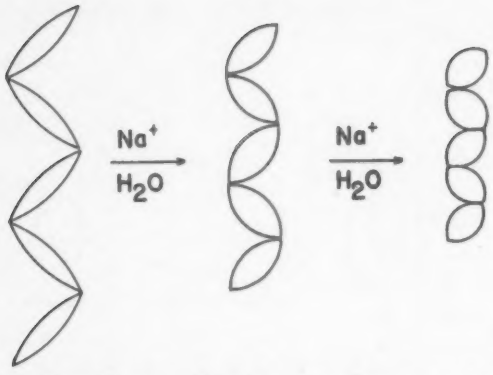


FIG. 5. Possible water logging of vascular smooth muscle cells, resulting in shortening.

changes in arterial walls as increased oxygen consumption and cytochrome oxidase activity,[8] and changed tonicity in response to the reduction of pH.[7] Experiments with vessel strips from normotensive animals indicate that hypertonic solutions, including those having high concentrations of sodium chloride, produce an increase in reactivity, and that the opposite holds true for hypotonic solutions, including such solutions low in sodium concentration.

The gradual increase in tension shown by strips from hypertensive animals when placed in hypertonic solutions, in contrast to the behavior of strips taken from normotensive animals, may be due to an imbibition of solute and water as a result of altered membrane permeability. As a consequence of this soaking up of water and ions or other solute, the normally thin, elongated, smooth muscle cells may become shorter and fatter, thereby exerting an apparent contractile tension (Fig. 5). This is in accordance with the reported observations that aortic strips from hypertensive animals contain more ions and water per weight of dry solid than do strips from normotensive animals. *In vivo* such water-logging would tend to narrow the lumen of vessels (as pointed out by Tobian[7]) and intensify the hypertension already existing. Since the plasma of animals with essential hypertension has been reported to contain higher sodium concentrations than the plasma of normotensive animals, an intensification of hypertension as a result of the imbibition of ions and water may be of some importance in the natural history of hypertension in human beings.

SUMMARY

Rats were rendered hypertensive either by the administration of DCA and salt or by renal constriction. Isometric tensions developed in strips of aorta from these rats, when exposed to epinephrine or levarterenol, were compared with the tensions in aortic strips from normotensive control rats The strips from the hypertensive animals responded, in general, with smaller contractile tensions than did those from the normotensive rats. Contractions of aortic strips from DCA-salt hypertensive rats were also compared with those of strips from control animals in the presence of solutions of altered sodium ion concentration and/or tonicity. The strips from hypertensive animals, in contrast to those from control animals, manifested a slow, prolonged increase in tension in the presence of solutions of elevated sodium ion concentration or tonicity, alone. Addition of epinephrine then caused relatively weak contractile responses in the strips from hypertensive rats while the strips from the normotensive rats contracted even more vigorously than when in normal solutions.

These results are interpreted to mean that as a consequence of hypertension, arterial walls became not only structurally but also functionally altered, and that the functional alteration includes a decreased reactivity to catecholamines and a changed contractile behavior in the presence of elevated sodium ion concentrations and/or hypertonic solutions.

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Role of Electrolytes in the Contractile Machinery of Vascular Smooth Muscle*

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ALTHOUGH THE investigator who undertakes an inquiry into the cause of the elevated arterial pressure in experimental hypertension should not ignore the possibility of an elevated cardiac output, his most promising avenue of research will be in the possible causes of an increase in total peripheral resistance. In organizing his approach to this problem he must recognize that total peripheral resistance may be elevated by any one of the following, reasonably well separable mechanisms (Fig. 1): (1) an increase in neurogenic constrictor traffic to the resistance vessels; (2) an increase in circulating humoral constrictor substances; (3) an increase in vascular smooth muscle responsiveness to the normal determinants of vascular smooth muscle tone; and (4) a change in structure of the vessel wall, increasing peripheral resistance.

Of these four possible causes of increased total peripheral resistance, the one that is probably most difficult to evaluate is the increase in vascular smooth muscle responsiveness. Yet a primary basis for the current seminar on the role of salt in cardiovascular hypertension is the possibility that an altered functional electrolyte composition in vascular smooth muscle is responsible for an exaggeration in the response of the muscle to normal vasoconstrictor stimuli.

Appraisal of the validity of this theory may be made by analysis of the relative electrolyte composition of blood vessels from normotensive and hypertensive animals or by evaluation of the effectiveness of imposed alterations in electrolyte composition on the contractile process in vascular smooth muscle. The current study, which is part of a broad program aimed at describing the contractile machinery of vascular smooth muscle, falls into the latter category. The theme of this presentation will emphasize the complexity of this problem and the superficial level of our current insight into it. The contractile process is quite like a jigsaw puzzle (Fig. 2) in which most of the pieces are not yet satisfactorily in place. These pieces consist of at least seven physiologically active ions: Na^+, K^+, H^+, Ca^{++}, Mg^{++}, Cl^- and HCO_3^-. A clue in properly positioning these pieces to make the final picture is the realization that there are at least four somewhat separable processes which play a role in the contraction and relaxation of the vascular smooth muscle cell. (1) Events in the cell membrane as they alter either electrochemical gradients or permeability to electrolytes and other vasoactive agents constitute the usual starting point for alterations in the contractile state of the cell. (2) A coupling process by which the influence of these membrane phenomena is transmitted to the contractile protein forms the second link in the chain of events. (3) The third process and the one responsible for the actual mechanical change is the chemomechanical transducing which is a property of the contractile protein. This change in mechanical state is presumably dependent on an energy source in organic phosphates. (4) Metabolic processes in the cell are responsible for the elaboration of these high energy phosphates.

The complexity of this picture and our current state of ignorance are emphasized by the realization that there is little if any adequate experimental evidence describing the role of any one of the physiologically active electrolytes in any one of these four processes. Somewhat better associations have been made between the various electrolytes and specific processes in skeletal, cardiac and even other smooth muscle.

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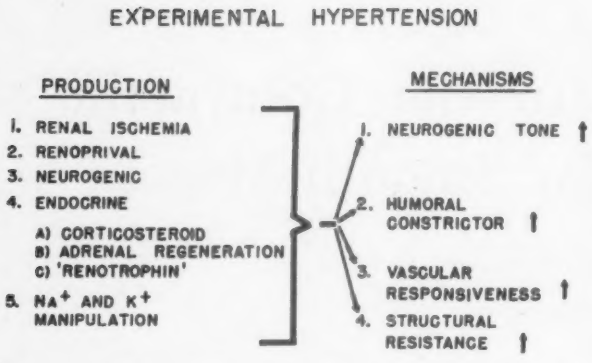


FIG. 1. Experimental hypertension; methods of production and possible mechanisms involved.

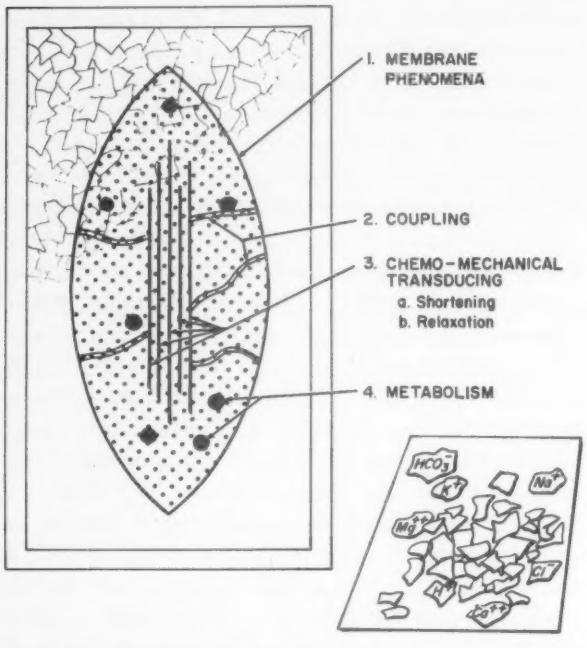


FIG. 2. Jigsaw puzzle representation of components of the contractile mechanism in a vascular smooth muscle cell. The object of the game is to fit the ion pieces (represented at the lower right of the figure) into the several processes (named at the right) which make up the contractile mechanism.

Our current impression of the role of these electrolytes in the mechanical response of vascular smooth muscle therefore arises largely from analogy from these other studies.

The pattern of our current approach to the problem has been to evaluate the effects of variations in the concentration of a single electrolyte on the mechanical performance of isolated vascular smooth muscle. Three objections to this type of study have been met, with varying levels of satisfaction: (1) It has been pointed out that such studies require the use of large blood vessels, the smooth muscle of which is not concerned in vascular resistance.

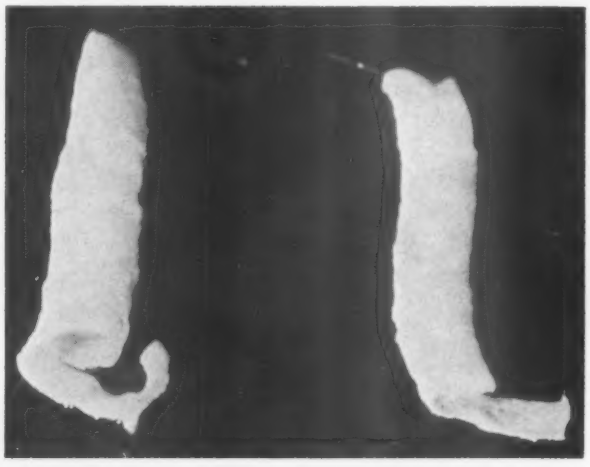


FIG. 3. Portion of aorta from normal (right) and hypertensive (left) rat showing helical strip cut from each.

We have met this objection by developing a technic which enables us to record tension from isolated vascular smooth muscle obtained from resistance vessels. (2) It is evident that the environment of the vascular smooth muscle cell in the isolated system must be different from that *in vivo*. It is also certain that both intraluminal and extraluminal factors *in vivo* must alter the response of the vascular smooth muscle cell. It must be realized that these same influences cannot be adequately controlled and therefore will superimpose their effects on that of the electrolyte being studied. Furthermore, although it is possible to measure changes in resistance in a vascular bed, it is impossible to extrapolate from these measurements definite information about active tension in the vascular smooth muscle cell. The isolated tissue therefore becomes a necessary starting point for securing this basic information. (3) The effect of a given shift in electrolyte composition in the environment of the isolated vascular smooth muscle gives little direct information related to the site of this influence in the contractile process. In their present form, therefore, these studies are merely empirical observations from which certain interpretations can be drawn. The need for caution in making such interpretations is emphasized by the fact that certain electrolyte shifts alter more than one of the phenomena involved. An example of such a complicating situation will be presented in which it is apparent that a unidirectional shift of potassium enhances vascular response by its effect on one mechanism while it depresses vascular response by its effect on another mechanism. The effect that

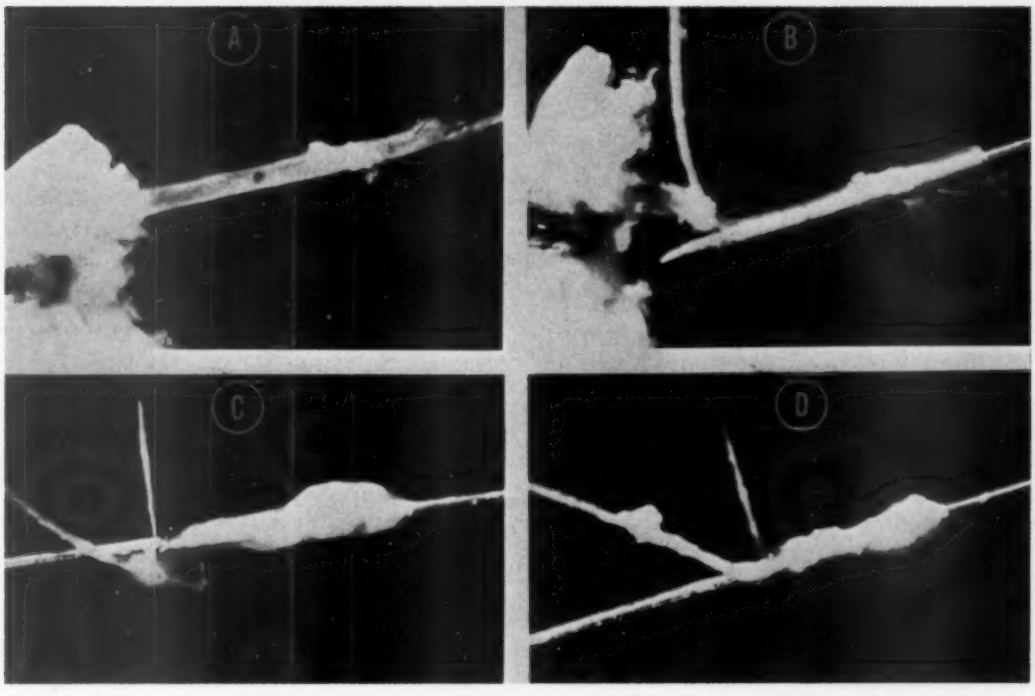


FIG. 4. Preparation of "arteriolar" strip. A, a small vessel (250 μ) is partially freed from surrounding mesentery (rabbit). B, a thread is knotted around the proximal end of the vessel and a fine rod is threaded through the vessel from the distal end, penetrating the wall near the knot. C, rod and vessel in place in lathe. The cutting blade may be seen near the thread. The "arteriole," on the rotating rod, is guided into the cutting blade by means of this thread. D, cutting of helical strip from "arteriole" is in progress. FROM: BOHR, D. F., GOULET, P. and TAQUINI, A. C., JR. *Angiology*. In press.[2]

will be evident from this shift in potassium concentration will therefore depend on which of the processes affected is the limiting factor for contraction.

METHODS

To prepare smooth muscle from large arteries for study in the isolated system, helical strips (Fig. 3) were obtained. Those illustrated are of rat aorta; those used in the current study were obtained primarily from rabbit aorta and from dog carotid. The strips were mounted in muscle chambers in a bath maintained at 38°C., pH 7.35 and aerated with 95 per cent oxygen and 5 per cent carbon dioxide. The composition of the bath in millimoles is as follows: NaCl, 118.9; KCl, 4.7; KH_2PO_4, 1.2; $MgSO_4$, 1.2; $NaHCO_3$, 14.9; dextrose, 5.6; $CaCl_2$, 2.5; sucrose, 49.9; and calcium disodium versenate, 0.026. Contractions of the muscle strips were recorded either isotonically, on smoked paper, or isometrically by means of a strain gauge tension transducer (Grass Model FT03). It has been noted that during a 2 hour incubation period the electrolyte composition and the responsiveness of such preparations reaches a stable level which persists for at least 6 hours.[1]

Similar strips of smooth muscle tissue from resistance vessels (200 to 300 μ diameter) were prepared by (1) threading a fine wire through the lumen of the vessel, (2) mounting the wire in the chucks of a jeweler's lathe, and (3) cutting a helical strip from the vessel wall with a razor blade mounted in a slide rest, as the wire rotates. This process is pictured in Figure 4, and is more fully described elsewhere.[2] Such strips, 100 μ wide and 1 mm. long, were mounted in the same manner as aortic strips and tension was recorded by means of a strain gauge. Small vessels obtained from the rabbit mesoappendix have been used for most of these studies; preliminary work has also been done on resistance vessels from the lung and brain. In some experiments two strips, one from a resistance vessel and one from a conduit vessel, shared a common bath, thus making possible a comparison of the responses of the two to the stimuli imposed.

RESULTS

Role of Potassium in the Contractile Response of Smooth Muscle from Large Conduit Vessels: We have made two studies, previously reported, on the effect of potassium on the responsiveness of smooth muscle from large vessels. In one[3] it was noted that the response of the isolated rabbit aorta strip to epinephrine stimulation varied directly with the potassium concentration in the bath, over a range of 0 to 9.4 mM

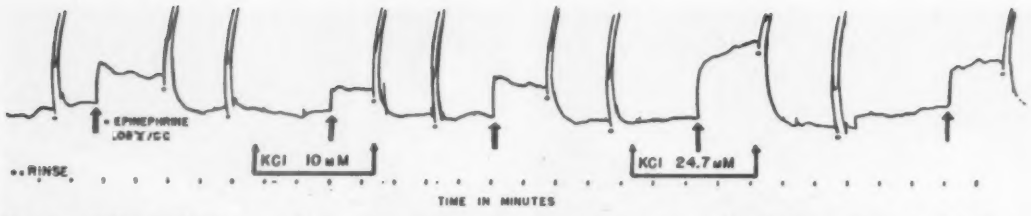


FIG. 5. Effect of high potassium on response of resistance vessel to epinephrine. Note the biphasic effect, a depression at 10 mM and a potentiation at 24.7 mM.

concentration. In a study reported just prior to this publication, Leonard[4] had noted a somewhat greater response of rabbit carotid tissue to electrical stimulation after the removal of potassium from the bath.

Our second study[1] was a more detailed analysis of the relationship between potassium and vascular responsiveness designed in part to resolve the apparent discrepancy between our results and those of Leonard. The basic objective was to differentiate between the effects of (1) intracellular potassium concentration, (2) extracellular potassium concentration and (3) the ratio between the two. Muscle strips (dog carotid) were stored at +4°C. for 48 hours; at the end of this time the intracellular potassium concentration was in equilibrium with that of the surrounding bath. Strips were then mounted in a bath at 38°C. and responses to electrical stimulation were recorded at 15 minute intervals until a maximum uniform responsiveness was reached. Strips so treated were analyzed for potassium concentration and extracellular water volume, and intracellular potassium concentration was calculated. Such studies were carried out with tissue in baths of different potassium concentrations (from 0 to 24 mM). It was possible thereby to associate both changes in vascular responsiveness and changes in baseline tension with each of the three parameters: (K_i), (K_o), $(K_i)/(K_o)$. The concentration of intracellular potassium was always greater when the amount of potassium in the bath was greater. Just the opposite was true for the ratio of internal to external potassium: when the concentration of potassium in the bath was highest (24 mM) the K_i/K_o ratio rose most slowly and reached the lowest steady state value. The following conclusions were reached in these studies: (1) an increase in intracellular potassium increases contractility, (2) an increase in intracellular potassium increases the rate of relaxation, (3) excitability is decreased by a K_i/K_o ratio above or below the optimal ratio, (4) the degree of tonic shortening depends on the K_i/K_o ratio and (5) contracture develops in a potassium-free environment. The results on which these conclusions are based constitute strong evidence that the potassium ion can influence vascular smooth muscle response both through its gradient across the cell membrane and by the direct action of its intracellular concentration. Furthermore, there is evidence that optimal K_i, K_o and K_i/K_o values exist and that when the levels are changed in either direction from the optimal, the performance of the muscle is impaired.

Role of Potassium in the Contractile Response of Smooth Muscle from Resistance Vessels: In earlier experiments with conduit vessels it had been noted that whenever the potassium concentration of the bath was increased above a physiologic level, the magnitude of the response to epinephrine was increased. The pattern of the effect of an increase in potassium concentration of the bath on the response of the resistance vessels to epinephrine stimulation is much more complex. The most common pattern is shown in Figure 5. When the potassium concentration of the bath was increased to 10 mM, the contractile response to epinephrine was less than that at control values (4.7 mM). When the potassium concentration was further increased to 24 mM, however, the expected potentiating effect of an elevated potassium concentration was evident. Although this is the usual pattern, in some preparations which have been studied the epinephrine response was potentiated at all levels of increased potassium concentration and in other preparations the epinephrine response was depressed at all levels of elevated potassium concentration. These observations constitute further evidence of at least a dual site of action of potassium, depressing at one site and potentiating at the other.

The implied difference between the smooth muscle of large and small blood vessels with regard to the effect of increased potassium con-

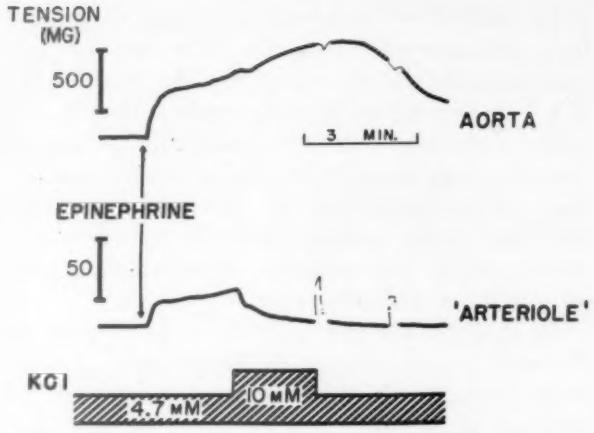


FIG. 6. Comparison of effects of high potassium on response of aorta and "arteriole" to epinephrine. Ten millimoles of potassium caused a potentiation of the aortic response and a depression of that of the resistance vessel.

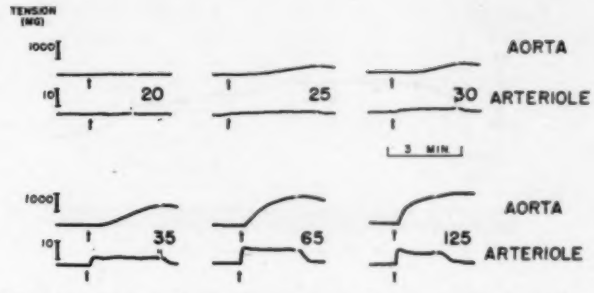


FIG. 7. Comparison of responses of aorta and "arteriole" to KCl; arrows indicate addition of KCl to the bath; large numbers indicate final KCl concentration in mM/L. (See text for significant differences.)

centration on the epinephrine response is emphasized by the result depicted in Figure 6. In this experiment, 3 minutes after the initiation of an epinephrine response the potassium concentration of the bath was increased to 10 mM. "Arteriole" and aorta were in the same bath. It is evident that in this preparation the increased potassium concentration caused a relaxation of the epinephrine contraction in the resistance vessel while it potentiated the epinephrine response in the aortic smooth muscle.

The difference in the effect of potassium on the two types of vascular smooth muscle is further emphasized in Figure 7. When potassium was added to the bath to give a final concentration of 25 mM/L or greater it caused contraction of the smooth muscle from both the resistance vessel and the aorta. However, two striking differences are evident between the responses of these two tissues. The response of the resistance vessel was rapid even at threshold concentrations while that of the aorta was slow and persisted throughout the observation period. The second difference is more obvious with strips in higher concentrations of potassium, where it is evident that the initial rapid contraction of the smooth muscle from the resistance vessels is interrupted by a secondary partial relaxation.

Effect of Steroids on the Response of Vascular Smooth Muscle to Epinephrine: In studies reported elsewhere[3,5] we have noted that when desoxycorticosterone was present in the bath in low concentration (10^{-7} to 10^{-5}), which caused no shortening of the aortic smooth muscle, it produced a potentiation of an epinephrine response. Six steroids were compared for their ability to produce this effect. Since different steroids have well defined effects on both electrolytes and organic metabolism, it might be expected that such a comparative study would give some clue to the means by which desoxycorticosterone is capable of producing a potentiation of the response of the aortic smooth muscle. Furthermore, if there were a parallelism between the potentiating ability of a particular steroid and its ability to induce experimental hypertension, such an observation would constitute indirect evidence that the agent could produce the hypertension by sensitizing the vascular smooth muscle to adrenergic responses. However, the results indicated that the relative potentiating action of the various steroids bore no relation to their known physiologic action or to their ability to produce hypertension.

Steroid potentiation of the epinephrine response was also demonstrated by a further contraction of the rabbit aorta when desoxycorticosterone was added during the plateau of an epinephrine response. Doubling the physiologic concentration of potassium produced a similar increase in response to epinephrine. As in the case of desoxycorticosterone, this concentration does not produce contraction of a relaxed aortic strip in the absence of epinephrine. We believe that the response of the aortic strip to epinephrine can be enhanced by decreasing (within limits) the ratio of potassium inside to potassium outside of the vascular smooth muscle cell. When potassium in the bath is increased, this ratio decreases immediately and the potentiation is completed very rapidly. However, when desoxycorticosterone is added the potentiation is very gradual. This is the type of potentiation that would be expected if it were paralleling a

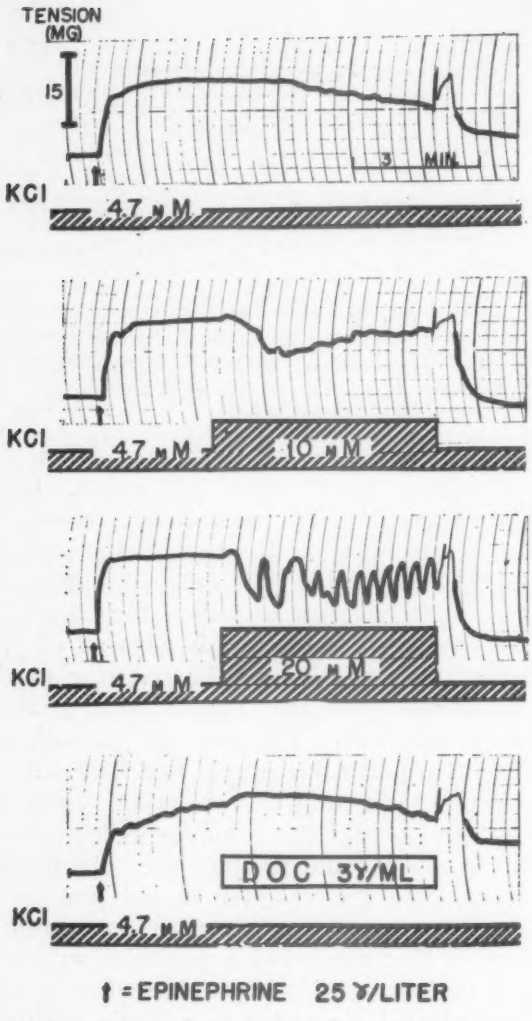


FIG. 8. Comparison of the effects of KCl and DOC on response of resistance vessel to epinephrine.

gradual and progressive decrease in K_i/K_o ratio. Since desoxycorticosterone is known to interfere with the entry of potassium into some cells,[6] there is some basis for the hypothesis that the mechanism of potentiation by the steroids is a gradual fall in intracellular potassium concentration, thus reducing the K_i/K_o ratio.

In view of our observations that an elevation in potassium concentration frequently reduced the response of the arteriolar smooth muscle, it seemed of interest to explore the action of desoxycorticosterone on the epinephrine response of these resistance vessels. Figure 8 is the record of such a study in which the typical depression of an epinephrine response was observed when the potassium concentration of the bath was increased. No such depression of an epinephrine response was observed when desoxycorticosterone was added to the same muscle preparation. This use of deoxycorticosterone as a clue for the positioning of a fragment of the jigsaw puzzle, relating the effect of potassium to the contractile process of vascular smooth muscle, demonstrates mainly that the relationships are extremely complex and that there is great individuality between the responses characteristic of vascular smooth muscle from different sites.

Effect of Sodium and Calcium on the Response of Vascular Smooth Muscle to Epinephrine: In an earlier study[3] we have demonstrated that an increase in sodium concentration in the surrounding bath causes a depression of the vascular smooth muscle response to epinephrine, whereas a decrease in sodium concentration below that of the normal bath results in a potentiation of the response. Recently we have observed similar effects in the response of smooth muscle from the resistance vessels to shifts in sodium concentration in the bath (Fig. 9); the potentiation associated with a decrease in sodium concentration is evident.

The requirement for calcium in the response of vascular smooth muscle to epinephrine seems to parallel its essential role in the contractile process of other muscle tissue. In Figure 10 it is evident that lack of calcium causes progressive decrease in response of smooth muscle from both the aorta and the resistance vessels. Much evidence has been advanced[7] associating the calcium ion with the coupling between the membrane excitatory process and the contractile protein. It has further been suggested[8] that in this coupling process, calcium cations compete with sodium cations for anionic binding sites. A decrease in sodium would make more of these anionic sites available to calcium and therefore enhance the contractile response. This hypothesis is in keeping with our observations on the effect of various sodium concentrations on the response of vascular smooth muscle. Admittedly such an interpretation is indirect; however, it attracts us as the only interpretation related to basic observations on the contractile process of muscle tissue which is in keeping with the common observation that the constrictor response of smooth muscle is potentiated by a decrease in sodium concentration.[9] Interpretations which relate the low sodium potentiation to a reduction in the Na_o/Na_i gradient[10] have no basis in our current understanding of the contractile process of muscle.

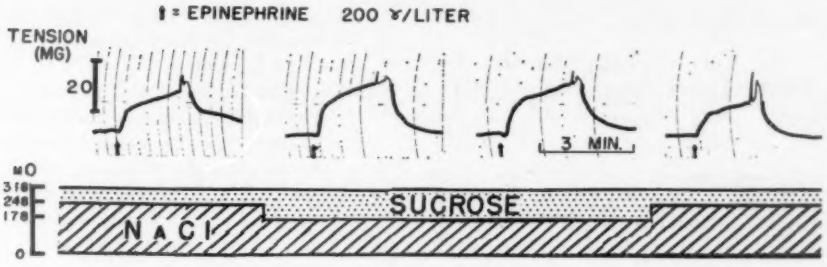


FIG. 9. Effect of low sodium on response of resistance vessel to epinephrine. The response is potentiated by a reduction in sodium concentration.

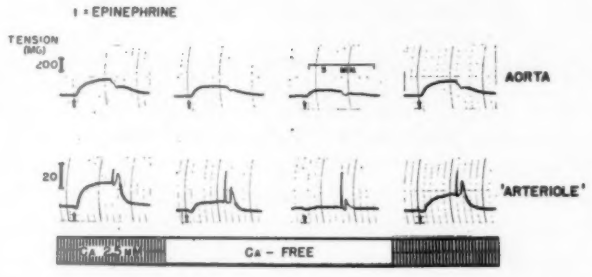


FIG. 10. Effect of no-calcium on response of aorta and "arteriole" to epinephrine. The response of both is depressed in the absence of calcium.

CONCLUSIONS

Finding the answer to any question must begin with the development of an understanding of the problems involved. It will be of great help in positioning the electrolyte fragments of the jigsaw puzzle that will picture the contractile process of vascular smooth muscle, to recognize the various components of the over-all contractile process. Major assistance in this understanding can also be found in the rapidly developing area of physiology of other types of muscle. This philosophic approach to the solution of the problem must be tempered by an expectation of real or apparent differences, not only between vascular smooth muscle and other muscle, but also among vascular smooth muscle preparations from different sources. When a mechanical response is used as a parameter for evaluating the effect of a certain ion, it must be realized that this parameter is the result of a chain of events and that the ion involved may influence several of the links of this chain. Evidence cited in the current study suggests that an increase in potassium concentration may enhance the function of one of these links and depress that of another. The net result, evidenced in the contractile response, will depend on the relative influence of the ion on the two links and also on the importance of the particular link as a "rate limiting" factor in the response.

SUMMARY

The following observations of the effect of imposed alteration in electrolyte composition on the contractility of vascular smooth muscle emphasized the complexity of the processes involved:

1. Studies based on the relation of changes in mechanical performance in response to changes in intracellular potassium (K_i) and in the K_i/K_o ratio constitute strong evidence that the potassium ion can influence vascular smooth muscle response both through its gradient across the cell membrane and by direct action of its intracellular concentration.

2. While an increase in potassium concentration in the bath causes only an increase in the magnitude of response of smooth muscle from large conduit vessels, the effect of an increase in potassium concentration on the response of resistance vessels is usually biphasic, small increases depressing and larger increases potentiating the response. These observations constitute further evidence of at least a dual action of potassium.

3. Six steroids were compared as to their ability to produce a potentiation of an epinephrine response. The relative potentiating action bore no relation to their known physiologic effects or to their ability to produce hypertension.

4. A decrease in sodium concentration in the bath causes an increase in the responsiveness of smooth muscle from both conduit and resistance vessels.

5. A decrease in calcium in the bath results in a decrease in the responsiveness of smooth muscle from both of these vessels.

Acknowledgment

We are indebted to Dr. Ruth McVaugh for her editorial contributions which converted our rough ideas to communicable concepts.

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A Closer Look at the Problem of Vascular Reactivity of Isolated Aortic Strips*

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ONE OF THE fundamental questions concerning the nature of hypertension, both experimental and clinical, is what is responsible for the greater degree of constriction of the arterioles in the hypertensive subject. There is much indirect evidence supporting the theory that the arterioles of the hypertensive person or animal are more sensitive to vascoconstrictor agents than those of the normotensive person or animal. However, direct proof is still lacking. On the assumption that the aorta of the rat might respond in a manner similar to that of the arterioles of the same animal, Redleaf and Tobian[1] and Mallov[2] have tested *in vitro* the responsiveness of a strip of rat aorta to norepinephrine, comparing strips from hypertensive rats with strips from normotensive rats. Both investigators found the aortic strips from hypertensive rats no more sensitive or actually less sensitive than the aortic strips from normal rats. These results cast some doubt on those theories which propose hyperresponsiveness of blood vessels as a causal factor in hypertension.

It occurred to us that the results of such experiments might be different if the possible influence of initial length on the responsiveness of the smooth muscle of the aortic strips were considered. The aortic wall of the hypertensive animal is continuously subjected to about twice the tension exerted upon the normal aortic wall (according to LaPlace's law, tension = pressure × radius); therefore, it might be supposed that the hypertensive vessel would have a higher optimum initial tension for exhibiting its maximum responsiveness than the normal vessel. It has been shown for various types of smooth muscle that, just as in the case of skeletal muscle, there is a length-tension curve with a maximal strength of isometric contraction at a certain initial length and a corresponding initial tension. This has been shown for uterine muscle by Csapo and Goodall,[3] for the retractor penis muscle by Winton[4] and for the pharyngeal smooth muscle of the snail by Abbott and Lowy.[5] More pertinent to the problem at hand, it has been shown by Ducret[6] to apply to strips of carotid artery when stimulated by epinephrine.

METHOD

To test our hypothesis, we have followed fairly closely the technic of Redleaf and Tobian,[1] cutting a thoracic aorta from a rat, into a helical strip and exposing the strip to norepinephrine (10^{-7} molar)in a bath of Krebs-Ringer solution containing Versene® (ethylenediaminetetraacetic acid tetrasodium salt) (10^{-5} molar). The bath fluid was aerated with 95 per cent oxygen, 5 per cent carbon dioxide and kept at a temperature of 36.5°C. In order to be sure of the width of the spiral strip it was trimmed to uniform dimensions by cutting along each side. The recording apparatus consisted of a flat steel band fixed at one end and attached at the other end to a lever arranged to amplify its movement. The aortic strip was fixed to a hook immersed in the bath and the other end was tied by nylon thread to the steel band at a point about 18 cm. from its point of fixation. The movements of the aortic strip were thus amplified about twenty-five times and recorded on a kymograph.

The length of the strip ranged from 30 to 36 mm. at zero tension. The contractions were nearly isometric; the maximum shortening which occurred being less than 2 per cent of the length of the strip. An important difference between our technic and that of Redleaf and Tobian[1] was that our rats were given a large dose of Nembutal® (pentobarbital sodium) (60 mg. per rat) prior to exsanguination. With our technic it was not necessary to use sodium nitrite to insure relaxation and responsiveness of the aortic strip. The strip was allowed to relax in the bath for $1^1/_2$ hours and was then tested at 45 minute intervals by the addition of norepinephrine to the bath. Fifteen minutes were allowed for full contraction to occur and then the bath fluid was replaced

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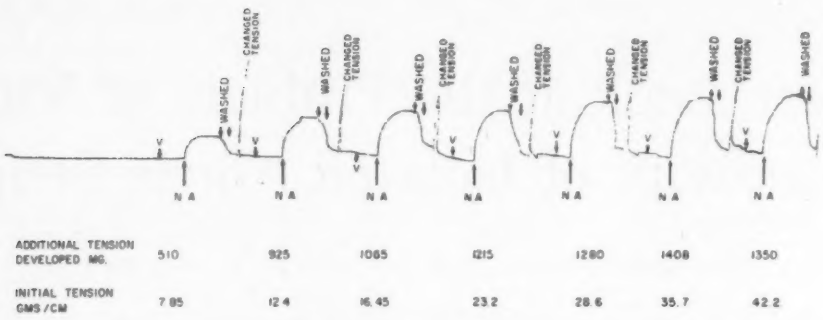


FIG. 1. Record of tension developed in a hypertensive rat aortic strip at successively increased initial tension. V = Versene added to bath to make a concentration of 10^{-5} molar. NA = noradrenaline added to bath to make a contraction of 10^{-7} molar. Time between additions of NA = 45 minutes.

twice by fresh Krebs-Ringer solution. Prior to each addition of norepinephrine the tension exerted upon the resting strip was set at some new value and the length of the strip was measured.

A total of eight experiments have been successfully carried out thus far. The aortas of four normotensive rats and of four hypertensive rats have been tested. The normotensive rats were three unoperated control animals and one animal which was not hypertensive in spite of constriction of the renal arteries. The hypertensive rats had been subjected to constriction of one renal artery and their hypertension had persisted for 3 to 4 months prior to the testing of their aortas.

RESULTS

The results (Figs. 1 and 2; Table I) indicate that the aorta of the hypertensive rat is more sensitive than that of the normotensive rat. The maximum tension exerted by the aorta of a hypertensive rat, at its optimal initial tension, when exposed to 10^{-7} molar norepinephrine is 1,227 mg. (average of four experiments). The maximum tension developed by the aorta of a normal rat at its optimum is 852 mg. (average of four experiments). These figures are based on a strip width of 3 mm. If the width of the resting strip differed from 3 mm. the actual tension developed was multiplied by the fraction 3 mm. divided by width in millimeters. The optimum initial tension, i.e., the tension at which the maximum response to norepinephrine was observed, was 36 gm. per cm. (average) in the aortas of the hypertensive rats and 19 gm. per cm. (average) in the aortas of the normotensive rats. The actual width of each strip at different lengths was measured at the end of each experiment.

TABLE I

Maximum Tension Developed (mg. per 3 mm. width)		Optimum Initial Tension (gm./cm.)	
Normal Rats	Hypertensive Rats	Normal Rats	Hypertensive Rats
900	1010	18	43
730	1500	12	36
870	937	28	32
910	1460	18	33
853*	1227*	19*	36*

* Average value.

CONCLUSIONS

Our results indicate that the aorta of a hypertensive rat is more sensitive to norepinephrine than is the aorta of a normotensive rat, in the sense that it exerts a greater force when excited by the same stimulus. However, this result does not take into account the thickness of the strip, only its length, width and the tension it develops. If the hypertensive aortic strip should be thicker than the normotensive, it might be that the greater force is

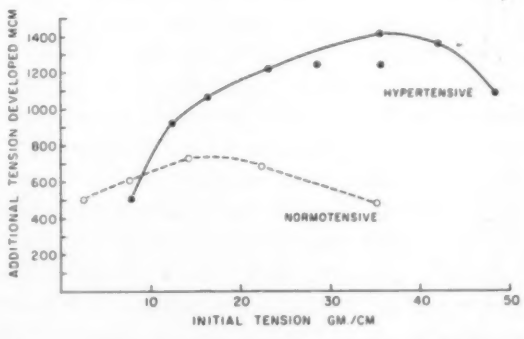


FIG. 2. Effect of initial tension on norepinephrine induced contraction of aortic strips from a hypertensive rat and a normotensive rat.

merely proportional to the greater amount of tissue. Preliminary measurements support this idea; the hypertensive aorta is, indeed, thicker-walled. This does not controvert our original conclusion that the hypertensive aorta is more sensitive; it means (if thickness and response are proportional) that the hypertensive aorta is more sensitive *because* it is thicker. We suspect that, per unit cross sectional area of smooth muscle tissue, the force developed on exposure to norepinephrine remains the same. This would fit very nicely into Conway's[7] concept of a nonspecific increase of sensitivity in the cardiovascular system of the hypertensive animal.

Summary

The responsiveness of isolated strips of rat aorta to norepinephrine was measured, a comparison being made between strips from rats with chronic (three to four month) renal hypertension and from rats with normal blood pressure. It was found that the strips from the hypertensive rats were more responsive than those from the normal rats. The maximum tension developed upon exposure to 10^{-7} molar norepinephrine in a bath of Krebs Ringer solution was 1,227 mg. and 852 mg. (average of the hypertensive and normotensive group respectively). It was also shown that the smooth muscle of the aortic strips exhibits a length-tension relationship with a definite optimum initial length and corresponding initial tension. It is necessary to set up a sufficient initial tension prior to adding the norepinephrine in order to reveal the true maximal responsiveness of the aortic strip. We believe that previous investigations comparing aortic strips from hypertensive and normotensive animals failed to reveal a greater responsiveness of the hypertensive because this necessary prerequisite was overlooked. The results reported here support the hypothesis that vascular hyperreactivity is an important and possibly a causal factor in hypertension.

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Panel Discussion

Chairman: Melvin J. Fregly

DISCUSSION OF PAPERS BY MENEELY, LEMLEY-STONE AND DARBY; OVERBECK, MOLNAR AND HADDY; MALLOV; BOHR AND GOULET; AND GORDON AND NOGUEIRA

Melvin Fregly (Gainesville, Fla.): The ground rules for this discussion will be that anyone may ask a question of any participant no matter when his paper has been given and you may carry over any questions or rebuttals to the afternoon session. Dr. Weller will lead off the discussion.

John Weller (Ann Arbor, Mich.): I wish to present some information concerning "Meneely-type" hypertension, if Dr. Meneely will forgive my using his name in that fashion. The studies were actually carried out by a medical student, Arthur Haight, and were concerned primarily with the study of the plasma and tissue electrolytes of rats given excess sodium chloride in their food. About 3 or 4 years ago Dr. Meneely told me that he had not had the opportunity to study the tissues of his rats although he had done some total body electrolyte studies.

I give this information rather apologetically because Dr. Meneely can talk in terms of 825 rats; whereas, we are talking of only thirty-five male Sprague-Dawley rats, divided into three groups and given three concentrations of salt 2.8, 5.6 and 8.4 per cent added to the food. We followed these rats for 55 weeks, a little over a year. With increasing percentages of salt in the food, the rats failed to gain weight normally. We tried to produce hypertension by this method, but unfortunately, over the period of 55 weeks, we did not find any differences in the mean

blood pressures of the three groups. I do not know the reason for our results differing from Dr. Meneely's, and I hope he will have some suggestions. Dr. Tobian told me he had added sodium chloride to the food of some rats for 2 months and didn't note any differences in blood pressure, but perhaps that was too short a time.

At the end of the 55 weeks, we examined these rats and found the following alterations in electrolytes: The plasma sodium was similar in all three groups, but the plasma potassium tended to be lower in the rats receiving the higher percentages of salt. The total water, chloride, sodium, potassium and calculated extracellular fluid volume (assuming all chloride is located extracellularly) in skeletal and heart muscle showed minor differences among the three groups. The methods were essentially those used by Lowry and Hasting (*J. Biol. Chem.*, 144: 637, 1942). It is very interesting that the aorta showed some definite trends. The total water content was lower in the rats ingesting the higher percentages of salt. In view of this finding, it was surprising to us that the chloride, sodium and potassium contents of aorta were higher in animals receiving the higher percentages of salt. I am talking in terms of per kilogram of fat-free, wet tissue. If one expresses this, as Dr. Tobian has, in terms of dry tissue, it would accentuate the differences. As the total water goes down, the concentration of the electrolytes goes up.

I would like to open the discussion by asking if others have carried out this type of salt-feeding experiment, which is an expensive and tedious one, as Dr. Meneely has indicated. I wonder if Dr. Meneely or others have done any further electrolyte studies on the tissues of their animals.

GEORGE MENEELY: I would like to comment only in part as later on in the seminar I will report on our tissue analyses of both sodium and potassium. I am surprised about the blood pressures because a great many other people have fed salt to rats and have gotten a rise in blood pressure. What method was used for measuring blood pressure?

JOHN WELLER: We were using the microphonic manometer technic of Friedman and Freed (*Proc. Soc. Exper. Biol. & Med.*, 70: 670, 1949).

GEORGE MENEELY: This has been used by us and by others who have found hypertension. I think Dr. Dahl has some hundreds of rats that have become hypertensive using salt and we have over a thousand rats made hypertensive by salt feeding. Our colleague at the Meharry Medical College, Dr. John Thomas, also has several hundred rats made hypertensive by this method. What strain of rats was used?

JOHN WELLER: Sprague-Dawley males. When we bought them they weighed 100 gm. Before we got started, they weighed 180 gm. We followed them from then on.

GEORGE MENEELY: Twelve months or 55 weeks is plenty of time. In 9 months they ought to be hypertensive.

JOHN WELLER: Your older rats still showed the elevation of pressure, did they not?

GEORGE MENEELY: Yes, we found they were hypertensive too. Did you look at the tissues microscopically?

JOHN WELLER: No, we did not.

GEORGE MENEELY: I would suppose you would find quite a bit of arteriolar disease.

FLOYD SKELTON (New Orleans, La.): In some of our early studies on adrenal regeneration hypertension we were struck by the effect of age on the development of this form of experimental hypertensive disease. When adrenal enucleation is performed on weanling rats of about 50 gm. body weight, hypertension develops quite readily. However, if the adrenals are enucleated when the rats are several weeks older, that is, at a body weight of 200 or 220 gm., adrenal regeneration hypertension does not develop. Under these conditions the saline intake of the older animals also fails to increase as it does in the young animals and may explain the inability of hypertensive disease to develop in such rats. The question still remains, however, as to why this occurs.

SIMON KOLETSKY (Cleveland, Ohio): How long did you follow them?

FLOYD SKELTON: We followed those for about 2 months only.

SIMON KOLETSKY: Was that adequate?

FLOYD SKELTON: Well, it was adequate for comparative purposes since our intent was to demonstrate that hypertension does not develop within the same period in young animals. Recently we have done some experiments in which the sodium content of the diet was varied. When the diet contained 2.5 per cent NaCl the hypertension did not develop in the control animals and the blood pressure of those bearing regenerating adrenals was only slightly higher. On a 5 per cent NaCl diet the blood pressure of control rats rose to minimal hypertensive levels, about the same as that observed in animals with regenerating adrenals and eating a 2.5 per cent sodium chloride diet. On the other hand, animals bearing regenerating adrenal tissue and eating a 5 per cent NaCl diet became markedly hypertensive with systolic blood pressures between 190 and 200 mm. Hg. When the diet contained 10 per cent NaCl, hypertension of about the same severity as that seen in the rats bearing a regenerating adrenal and eating the 5 per cent NaCl diet developed in control animals. Thus, there seems to be an additive effect between the hypertensive potential of salt alone and adrenal regeneration alone. The presence of regenerating adrenal cortical tissue just about doubles the hypertensive potential of any given dietary intake of NaCl

SIMON KOLETSKY: I will report some data on rats which drink salt instead of eating it; in other words,

long-term salt hypertension with animals having intact kidneys and given 1 per cent salt to drink instead of water. It might be appropriate to make a few references to this in relation to the points that have arisen.

In our experience, no matter how much we load rats with salt, it is very difficult to achieve a 100 per cent success in elevating the pressure. For example, in rats drinking saline all their lives, the incidence of hypertension in about 60 per cent. This means that hypertensive cardiovascular disease did not develop in 40 per cent which have been "drowned" with salt. There are vagaries that govern the consideration of incidence. If the diet is of the standard pellet form and a rat drinks 1 per cent NaCl, the total amount of salt intake daily would be something like 2 gm., which is in the low range of salt diet Dr. Meneely is talking about. These rats usually have polydypsia and drink about 100 cc. of 1 per cent saline daily. This has been a highly effective method of producing hypertensive cardiovascular renal disease and we should emphasize the vascular component. We ought to keep in mind that the hypertension is only one of the lesions that is being produced.

I would like to refer to Dr. Weller's observation on electrolytes. That the heart and skeletal muscle may not be significantly altered with respect to electrolyte content has been the experience of a number of people including a brief venture of our own into this area. Tissues of hypertensive rats vary in electrolyte concentration, and apparently certain tissues, skeletal muscle being one of them, may not be significantly altered. For example, we have not been able to demonstrate an increase in the water content of the heart in hypertensive rats, whereas the aorta and the mesenteric vascular bed show a very significant accumulation of water plus a significant accumulation of potassium. Our data on the mesenteric arteries, as I will report later, verify Dr. Weller's data. In the vascular bed, there are certain specific changes in hypertensive rats that seem to be significant.

LEWIS DAHL (Upton, New York): We have explored the question of age and I think it is critical. If we were to use a small group such as Dr. Weller used and wait until they weighed 200 gm., we would expect to get not more than one or two with a modest hypertension even within a year. If he had taken those same animals and started them as weanlings, based on our experience with female Sprague-Dawley rats, he would have found 60 to 75 per cent with some degree of hypertension at the end of 1 year.

Regarding this "concentration game," I think that the day of concentration as an indication of some kind of disease is, for all practical purposes, over. It has played an important role up to the present time because we did not have better methods of actually studying what was going on. But the failure to find differences in concentration of ions does not indicate that these noxious agents do not play an important role in the disease process. At the elementary level, if you were to study an animal that had received a good many "r" of radiation, you would not be able to find "r" in the tissue, but you would find a good deal of damage. By the same token, in diabetes concentration frequently does not help you very much, but when you go over to a more dynamic means of measuring blood sugar, you do find that there is evidence of disease. I would like to conclude by making an appeal to something dynamic, like flux, which might be more important to study than concentration.

ARTHUR GROLLMAN (Dallas, Texas): The use of isolated tissues in the attempt to elucidate the pathogenesis of hypertension suffers from a very fundamental weakness. You are studying the end result of disease! One might as well study the tissues of a drowned man to see what motivated his jumping into the water! I think we can accept the view that hypertension is a systemic disease which has caused the changes which are being observed in the tissues. The contradiction in the various findings reported this morning reflects the fundamental weakness in such studies. For example, Dr. Haddy's work would certainly cast doubt on the theories expressed regarding the significance of small sodium differences inside and outside of the arterial walls. Likewise, Dr. Mallov's results cast doubt on the significance of the claim that the blood vessels are more reactive in hypertension! Before one can imply the genesis, one should study, not the end result of the process which we know has occurred, but vessels in the animal before hypertension has developed. You will say this is impossible, but it can be done. It has been shown this morning that the younger the animal the easier it is to induce hypertension and I think this is a very vital point. Start before you wean the rats and you will get a higher percentage of hypertension. When you feed salt, or deprive the rats of potassium or choline, or you do any of a variety of procedures (these are the three we have used), these animals will have hypertension when they reach 6 months to a year in age. These are the kinds of rats you ought to utilize. Then, if you can detect some difference in reactivity, difference in composition, etc., one is justified in saying something about the relationship of these findings to the pathogenesis of hypertension; otherwise, the results may be interesting and the work commendable, but they offer no grounds for implying any pathogenetic relationship to hypertension.

SYDNEY FRIEDMAN (Vancouver, Canada): With regard to the work on salt-feeding hypertension, I would like to call attention to a point which McCance and Morrison (*Quart. J. Exper. Physiol.*, 41: 365, 1956) raised some time ago with regard to experiments of this type which contain a double variable. The variables here are salt and water. It is quite true that the animal fed more salt, drinks more. In my limited experience I have noticed that this does not quite cover the rat's extra intake of salt as it keeps

going up the scale. Has anyone reversed the field and looked at the water in relation to salt?

With regard to Dr. Haddy's elegant work, I would like to underline something which Dr. Haddy himself did mention, that is, the importance of not confusing the data which are valid and the interpretations which may be drawn from them. There is no question of the validity of his data. Many people agree with this point about hyperosmotic loading and the effects on peripheral resistance. To mention a few of the individual items, we can agree that the hyperosmotic effect can clearly not be differentiated from an effect on the intracellular concentration of ions, either sodium or potassium, as Dr. Haddy pointed out. The infusion of isotonic KCl raised no tonicity problem whatsoever, but when viewed in the light of current theories of ionic distributions and electrical potentials, it is quite clear that an effect of potassium is not to be expected if potassium concentration is raised to only 6 or 7 mEq. per L. Its depolarizing effect becomes logarithmic in isolated tissues when the concentration reaches 30 mEq. per L., which is very high. It only begins to show up at about 10 mEq. per L. The importance of this is not to decry the experiment, but to point out that the experiment is limited. One cannot raise the potassium concentration to 10 mEq. per L. or above *in vivo* because then one gets a systemic effect and defeats the purpose of the whole experiment. So, the procedure is not amenable to this type of experimentation. In a limited trial which we made using sodium electrodes in a setup similar to Dr. Haddy's, sodium and potassium electrodes were placed in the venous effluent and various ions in similar concentrations were infused into the hind limb of a dog. We found that it is totally impossible from any rule we know to predict what will actually react the cell in regard to what one puts in at one end. We have been surprised quite often. You cannot alter potassium without manipulating water and sodium and you cannot manipulate sodium without manipulating potassium and water; and so it goes, round and round. When you add this to the problem of the events inside the cell, we can see that the interpretation of perfusion experiments is valid as far as it goes, but must not be pushed to the point of having direct reference to the specific transmembrane ionic distributions involved. Dr. Haddy made this point in summarizing his own work and pointed out the possibilities that one has to consider as to how this is working.

Dr. Bohr raised several points. He has used a rather nice technic of cooling and rewarming, a familiar biochemical technic, for causing a shift in the dynamic equilibrium inside and outside the cell. I wanted to ask him whether these vessels constrict in the cold; we noted that the vessels constricted as potassium leached out of cells in the cooled tissue. The sodium presumably enters the cells and then when one rewarms the tissues and gains back the potassium, the sodium comes out.

Now as to technic in general—Dr. Bohr's point about using an arteriole if possible is, I think, essential. One has to be careful with aorta strip-taking. Even with a small vessel you may still be in difficulties because of not applying the natural manner in which those vessels work. As an anatomist, I may be forgiven if I remind you all that for a muscle to exert its function it must have an origin and an insertion. If you have smooth muscle cells divorced from both origin and insertion, no matter how one cell pulls on another, their insertion has been altered. Burton and Stinson (*J. Physiol.*, 153: 290, 1960) have drawn attention to this. They have returned to using rabbit ears. I have a longer background perhaps in spending time on this technic and I don't think I would like to start on rabbit ears again, but he does underline the problem which I think is an important one.

DAVID BOHR: I would like to comment on the constriction in the cold; actually our vessels relax in the cold. Incidentally, we use rings of tissue as well as helical strips and with similar results. We put a hook on either side of the ring so that their proper geometry should be maintained.

I feel advised to defend the isolated "vesselologist" against Dr. Grollman's philosophy about drowning and hypertension. If you examine a drowned man to find why he is dead, you find that his heart isn't beating and that he isn't breathing and this is the reason he is dead. If you examine a hypertensive subject, the reason you are investigating is to find the hemodynamic basis for the maintained pressure elevation. Why is the total peripheral resistance elevated in this subject whose pressure is still up? This is our concern.

EDWARD RADFORD (Boston, Mass.): Apropos of water and electrolyte, I would like to ask the "vesselologists" a question. Is this increasing vessel cell mass that is described hypertrophy or is it hyperplasia?

DAVID GORDON: One of the references I looked up prior to coming here was by Kernohan and associates (*Arch. Int. Med.*, 44: 395, 1929). It is a histopathologic study of arterioles in hypertension. They found both hypertrophy and hyperplasia. There were more nuclei. The cross section of the vessel structure showed an increased thickness of the media. It is probably both.

FRANCIS HADDY: I agree in general with the remarks of Drs. Friedman and Bohr. However, I would like to continue Dr. Friedman's discussion of potassium. We observe a measurable change in resistance to flow through the limb when we raise the serum potassium level over the range of 4 to 5 mEq. per L. In other words, changing potassium concentration from the normal level of 4 up to a level of 5, a change of just 1 mEq. per L., will produce a measurable decrease in resistance to flow. When we reach a range above 8 mEq. per L., we observe a reversal of response; resistance then starts to increase again and may reach a level higher than the control value.

Dr. Meneely, has anyone ever given rats or any

other animal a hypertonic solution of dextrose for periods equivalent to those you gave solutions of sodium chloride? In other words, has anyone given equally hypertonic dextrose and followed blood pressures of rats for many months to see if hypertension develops in these animals? I think the effect of sodium chloride is indirect through its ability to move water and that the same results might be achieved with any hypertonic solution.

GEORGE MENEELY: You understand we *fed* rats salt; they *drank* distilled, demineralized water. Someone asked me what about the fluid, and that is a good question. We designed an experiment but never did it; that is, to see if we could vary the water without varying other things. Salt does vary water intake but it varies a lot of other things too; the rats themselves are variable. We thought of taking some soluble food and providing it for different animals in successive dilutions, a purely liquid diet. In order to get calories, the rats would have to take additional fluid. Perhaps this would do it. It may be that something is being washed out with all the extra water.

Another slant on this is an experiment which we designed but did not do; that is, a study of the gastrointestinal flora. In the last analysis, salt in the gut may be an important contributing factor. The greatest amounts of salt are ingested via food in which salt is used as a preservative. The highly salted foods do not grow the same flora that grow with unsalted foods. It might be that the activities of the micro-organisms in the gastrointestinal tract are to blame for the results. It's a possibility.

CHARLES HALL (Galveston, Texas): Dr. Weller stated that the tissues were examined microscopically. Have you weighed the hearts? We have done this, and we and others have noted that hypertensive animals tend to have large hearts, particularly large left ventricles.

I agree with Dr. Grollman that if one is looking at a hyperplastic and hypertrophic aorta resulting from sustained high blood pressure over a long time, one cannot expect to find in that tissue either the cause of hypertension or the factor which caused the change in the vessels. That one can expect to find how much such a vessel must contribute to a sustained high blood pressure seems reasonable, but since the vessel change itself is a result of high blood pressure, I don't see how we can find in it the cause of high blood pressure.

JOHN WELLER: We did not weigh the tissues or examine them microscopically because Dr. Meneely's group had done this so thoroughly. Our study was not intended to repeat what Dr. Meneely had done. I'm glad my provocative remarks stirred things up a bit. Having made them, I'd like to soften them. I think there are many reasons why we did not get hypertensive animals; I don't think that is the important thing about the experiment. I agree with Dr. Koletsky that the saline drinking water experiments are quite effective; we too had about two out of three animals in which elevated pressure with this type of procedure developed. I can comment on our tissue findings in these animals after he tells about his work later today.

Dr. Grollman, I was not implying pathogenesis, but I think it is interesting that sodium, potassium and chloride were increased in the aortae of animals fed high salt diets as well as of those drinking sodium chloride solutions. These animals are nonhypertensive in the first instance and hypertensive in the second. In both groups we have findings similar to what Dr. Tobian found in many different types of experimental hypertension.

LOUIS TOBIAN (Minneapolis, Minn.): We were discussing the salt versus the water intake. Rodbard (*Proc. Council High Blood Press. Res.*, 6: 7, 1957) varied the water intake in relation to salt in chickens eating a lot of salt and noted that these were hypertensive whether or not the salt was combined with a lot of water. In other words, hypertension resulted both when the salt was isotonic and when it was hypertonic.

Dr. Radford brought up the question of the effect of hypertrophy on salt concentration in the little vessels. We have recently completed a study in which a group of both normotensive and hypertensive animals had a comparable degree of small vessel hypertrophy. Therefore, we could compare the effect of hypertension or the lack of it on vessels that were similarly hypertrophied. The hypertensive vessels did have more sodium than the vessels of the normotensive animals even though the degree of hypertrophy was the same.

HOWARD SWANN (Galveston, Texas): I can't resist playing a little game of one-upmanship on Dr. Friedman since he is so widely read. The question of how hypertensive rats handle salt and water was investigated by Ezrow and Sapirstein (*Am. J. Physiol.*, 194: 436, 1958).

Sodium and Potassium Exchanges and Peripheral Vascular Resistance*

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Vancouver, Canada

IT IS NOW well established that salt plays a central role in the hypertensive process. A half century of indirect evidence obtained from both animals and man has culminated in the effective use of salt-depleting agents as standard therapy in the treatment of the hypertensive patient.

Much less progress, however, has been made in understanding the mechanisms underlying the evident relation between hypertension and sodium. Tobian and Redleaf[1] have suggested the intriguing possibility that the intracellular accumulation of sodium in vascular walls might cause water logging and mechanically narrow the lumen of peripheral vessels. Raab[2] has suggested that an increase in intracellular sodium relative to extracellular sodium could increase the sensitivity of vessels to catecholamines and this might underly the hypertensive process. We have considered the dynamic equilibrium between extracellular and intracellular ion distribution to be itself a sufficient determinant of vascular tension.[3] The idea, implicit in our position, that membrane polarization is related to tonus was first explicitly stated by Bacq and Monnier[4] 25 years ago and has since had many advocates.[5]

It is against the background of these related theories that we propose to discuss the investigation of the association between acute changes in blood pressure and exchange of electrolytes. Although these studies are all comparatively recent and stem from different laboratories, the findings are quite clear cut and fit neatly together.

SERUM K AND NA FOLLOWING VASOPRESSOR DRUGS

Perhaps the earliest report of a relation between ionic concentration in the serum and a pressor agent was that of D'Silva[6] in 1934. He reported that following the intravenous injection of 50 μg. of epinephrine or ten units of Pitressin® (vasopressin) in the cat, serum potassium rose sharply as much as 3 mEq. per L. within 1 minute. Since these massive doses also caused a rise in blood sugar, he related the potassium rise to the glycogenolytic effect of the injections rather than to the blood pressure effect. This explanation for the rise of potassium remained unchallenged and uncritically accepted for almost two decades.

In 1953, O'Brien, Murphy and Meek[7] obtained curves showing the rise of plasma potassium after rather low doses of norepinephrine, 5 μg. per kg., in dogs (Fig. 1). Although norepinephrine does not have any marked effect on the mobilization of glucose and although these authors pointed out that it is blocked by Dibenamine,® which would not block a glycogenolytic effect, the original explanation still persisted. O'Brien and his associates also pointed out that the choice of anesthetic modified the effects (Fig. 2), ether being the worst as far as blurring the effect, cyclopropane affecting it least, and Nembutal® (pentobarbital sodium) being a close second best. These important observations were, unfortunately, ignored by most later workers including ourselves. (In our more recent studies we have found the effects considerably sharpened if a barbiturate mixture is used instead of ether.)

In the next year, Muirhead, Goth and Jones[8] restudied the problem. They administered norepinephrine by infusion in total doses of 1 to 7 mg. per kg. in 50 to 180 ml. of saline over periods ranging from 20 to 50 minutes. Concerning their results they wrote: "In many of the experiments the sodium curve represents an

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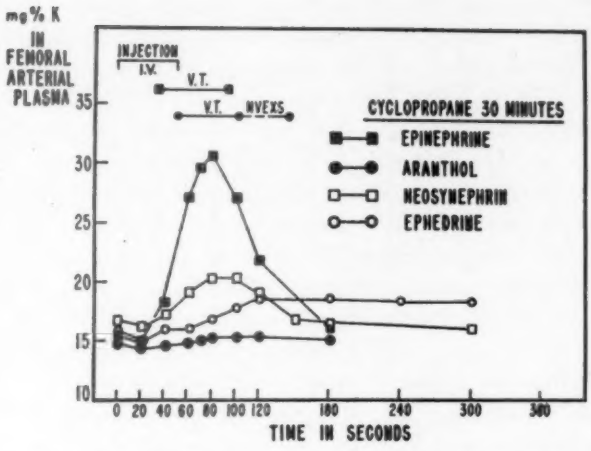


FIG. 1. Effect of a series of sympathomimetic amines on plasma K concentration in the dog. VT = ventricular tachycardia; NVEXS = numerous ventricular extrasystoles. FROM: O'BRIEN, G. S., MURPHY, Q. R., JR. and MEEK, W. J. *J. Pharmacol. & Exper. Therap.*, 109: 453, 1953.[7]

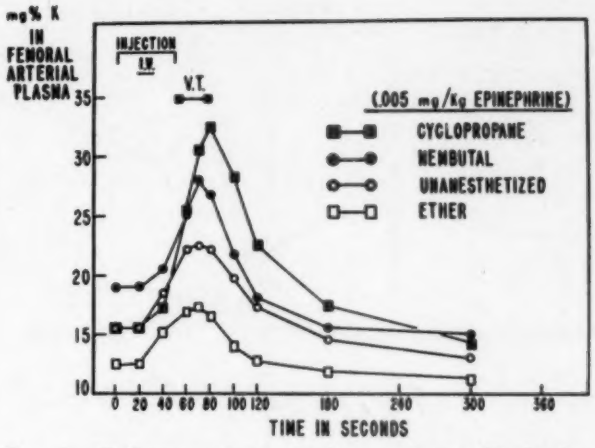


FIG. 2. Influence of anesthesia on plasma K rise induced by epinephrine in the dog. (Notation and reference as in Figure 1.)

approximate mirror image of the blood pressure curve. In most of the experiments the changes of potassium were not as pronounced as those of sodium. In addition there seemed to be little if any correlation between blood pressure and plasma potassium. The latter is in contrast to the variations in sodium levels which reflected even sudden changes in blood pressure." No real change in radiosulfate space or in chloride concentration was observed. These observations did not have the impact they ought to have had, for the doses used were very large.

Arterial Wall Sodium and Blood Pressure: Tobian and Fox[9] then approached the problem directly and analyzed segments of the femoral artery of the dog before and after infusing sufficient norepinephrine to maintain a blood pressure elevation for 30 minutes. A consistent fall in arterial potassium and a less consistent gain in sodium was observed. They believed these changes represented a fall in K_i and rise in Na_i but the authors tended to underestimate the importance of the sodium change since it was less consistent. In our view, the difficulties inherent in such tissue analysis and their basic range of error makes it highly significant that even this trend for a sodium increase was observed; in fact, a sizeable gain in sodium was noted in nine of twelve dogs. In the light of later evidence, we must conclude that a fall in K_i and a real gain in Na_i, probably with water, did actually occur.

SALT AND WATER EXCHANGE AND BLOOD PRESSURE

Shortly thereafter, following up the possibility that Pitressin might have an extrarenal action, we observed that this agent caused a shift of water out of the extracellular space in the bilaterally nephrectomized rat. In a more detailed study,[10] we found that sodium also left the extracellular space in association with, but in excess of, water so that there was a meas-

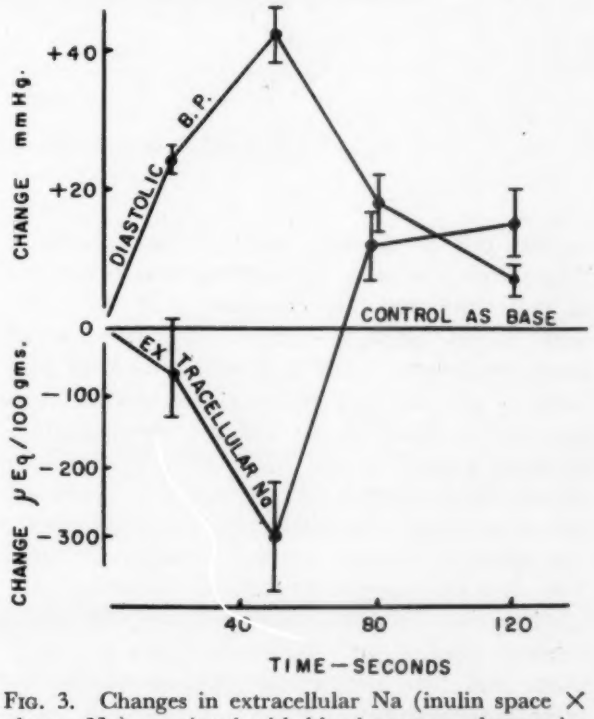


FIG. 3. Changes in extracellular Na (inulin space × plasma Na) associated with blood pressure changes induced by angiotensin in the rat. Graphed from data in: FRIEDMAN, S. M., FRIEDMAN, C. L. and NAKASHIMA, M. *Nature, London*, 180: 194, 1957.[12]

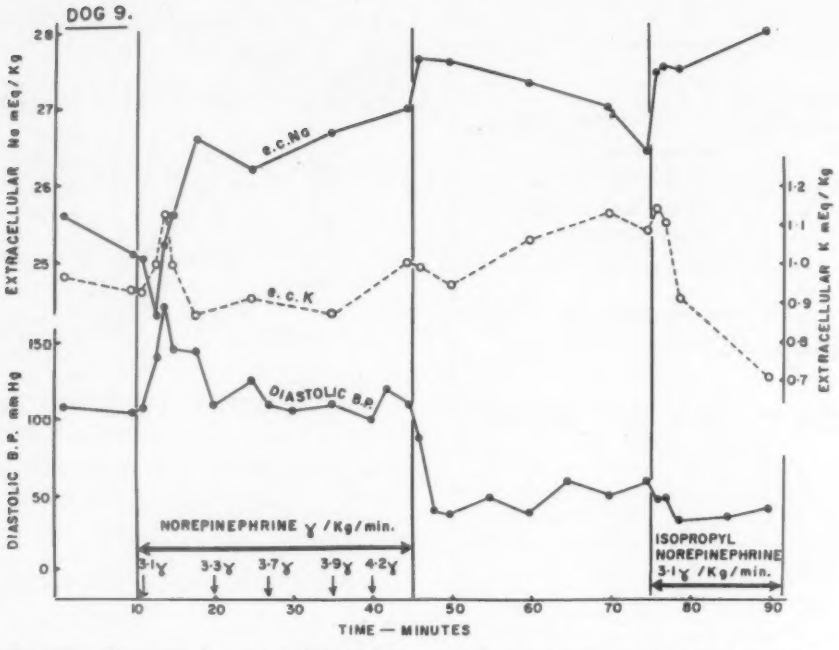


FIG. 4. Changes in extracellular Na and K associated with blood pressure changes in the dog. FROM: FRIEDMAN, S. M., BUTT, R. M. and FRIEDMAN, C. L. *Am. J. Physiol.*, 190: 507, 1957.[16]

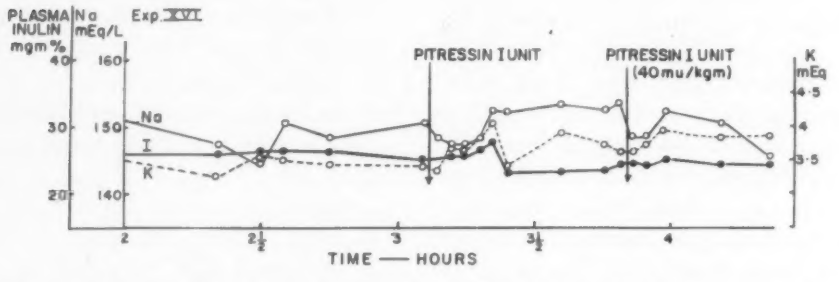


FIG. 5. Effect of Pitressin on plasma Na and K and inulin concentrations in the conscious dog.

urable fall in plasma sodium concentration. The relation of dose to response was presented at this time and the correlation of the shifts with blood pressure noted. In interpreting these exchanges of salt and water, we took into account the changes which other workers had previously observed to follow administration of norepinephrine and hypothesized that both sets of observations could be related by a general rule that blood pressure regulation depends on the sodium transfer systems, broadly defined. The rise in plasma potassium following administration of Pitressin was considered an integral part of the phenomenon but left aside from this first theoretical approximation for later consideration.

In these first studies we overestimated the absolute magnitude of the water shift that follows the administration of Pitressin. This was corrected in subsequent studies. The effects of norepinephrine on sodium, potassium, and inulin space in the nephrectomized rat were then compared with those produced by Pitressin and again a net loss of extracellular sodium was observed in association with the rise in blood pressure.[11] Angiotensin was then compared with Pitressin in the nephrectomized rat (Fig. 3). Both agents given intravenously produced a measurable fall in plasma sodium concentration and a fall in extracellular fluid volume (inulin) associated with the rapid rise of blood pressure. While Pitressin produced a measurable increase in extracellular potassium, angiotensin did not.

It was clear at this time, atl east for norepinephrine, that the fall in sodium and water and the rise in potassium which we were measuring in the extracellular compartment of the

rat corresponded qualitatively to the gain in sodium and loss in potassium which Tobian and Fox[9] had measured in the femoral artery of the dog. Daniel, Dawkins and Hunt[13] then injected a pressor dose of norepinephrine within the physiologic range of 1 μg. per kg. in the rat. They found that the aorta was rapidly depleted of potassium while sodium tended to increase. This is surprisingly good confirmation in view of the fact that the sodium shift is probably partly obscured by a movement of water which these workers could not measure.

Subsequently this group[14] studied the effects of isoproterenol, a peripheral vasodilator, on aorta electrolytes in the rat. They concluded from the variations in sodium in the aorta that during blood pressure changes, sodium moves into (rising blood pressure) and out of (falling blood pressure) vascular muscle cells.

In the rat, studies of changes in plasma sodium, potassium and inulin space during changes in blood pressure are technically difficult because each step in drug dose or time interval requires the use of separate groups of animals. To circumvent this, as well as to extend the observations to the dog, we[15] studied

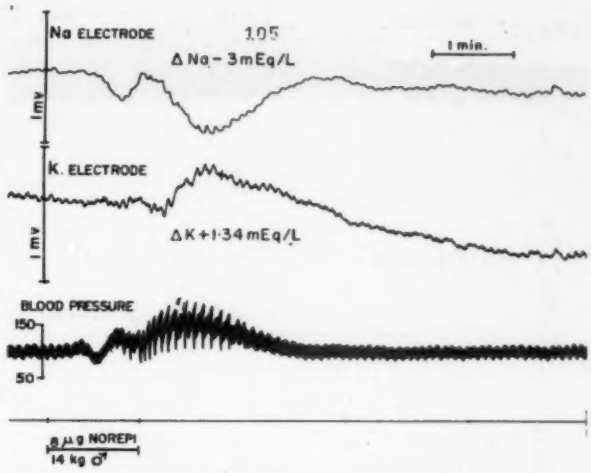


FIG. 6. Changes in blood (Na^+) and (K^+) monitored with the Na electrode (Na/K = 250/1) and K electrode (K/Na = 5/1) in the dog during systemic blood pressure rise induced with norepinephrine. FROM: FRIEDMAN, S. M., JAMIESON, J. D., NAKASHIMA, M. and FRIEDMAN, C. L. *Proc. Council High Blood Pressure Res.*, 8: 57, 1959.[17]

the problem in the bilaterally nephrectomized dog using norepinephrine, isoproterenol, angiotensin and Pitressin (Fig. 4). We found that the calculated extracellular sodium (product of inulin space and plasma sodium) declined as

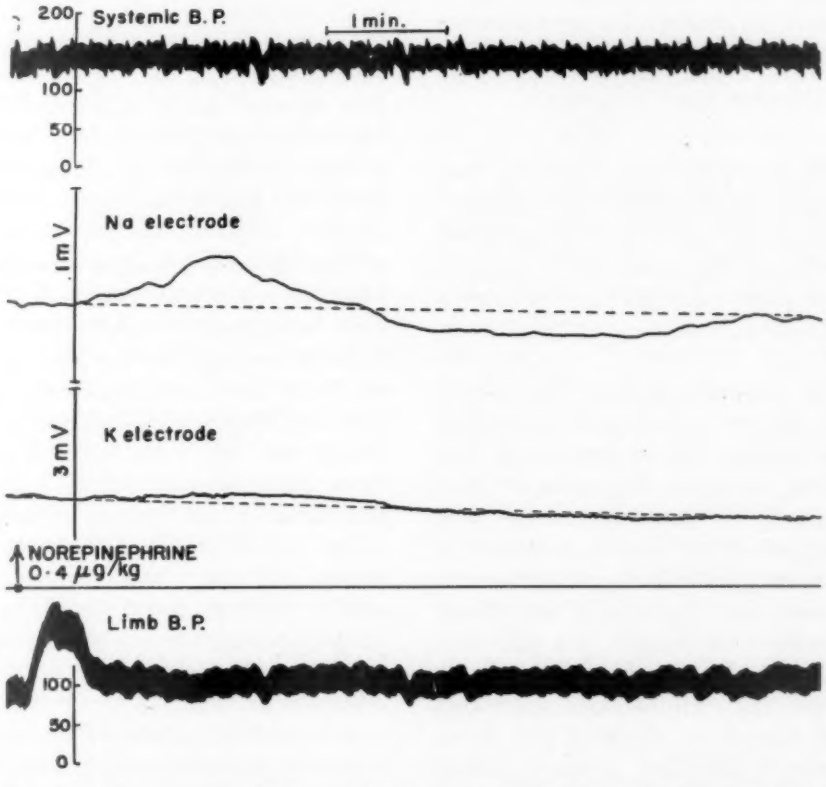


FIG. 7. Limb venous (Na^+) and (K^+) in the dog following intraarterial norepinephrine. Controlled arterial inflow and outflow rates. FROM: JAMIESON, J. D. and FRIEDMAN, S. M. *Circulation Res.* In press.[18]

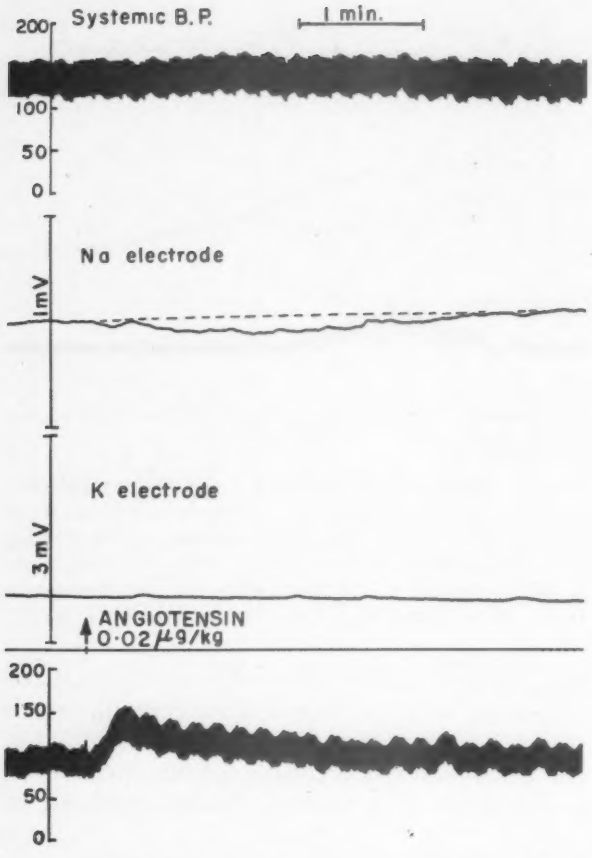


FIG. 8. Limb venous (Na^+) and (K^+) in the dog following intraarterial angiotensin. Controlled arterial inflow and outflow rates. FROM: JAMIESON, J. D. and FRIEDMAN, S. M. *Circulation Res.* In press.[18]

pressure rose and increased as it fell; the two measurements consistently formed mirror images. Calculated extracellular potassium in general moved inversely to sodium and hence parallel with the pressure except in the case of angiotensin in which, as in the rat, no potassium shift was found.

In the case of norepinephrine, the simple measurement of plasma sodium was an inconsistent index of sodium movement since the real decrease in this ion is partially masked by a movement of water in the same direction. For the same reason, potassium concentration is a consistent but inaccurate estimate of potassium movement because the change is magnified by inverse movement of water. In the case of Pitressin, although both sodium and water move out of the extracellular compartment, the sodium shift is well in excess of the water so that, if the dose is adequate, a fall in plasma sodium is readily observed. These findings are remarkably similar to those obtained in the rat (Fig. 5).

Na AND K ELECTRODES MONITORING AND ARTERIAL TENSION

Recently, the sodium and potassium electrodes have been applied to this problem. In the first experiments[16] we used only a sodium electrode interposed into the femoral artery of the dog. The aim was to determine whether pressor and depressor agents actually shift sodium levels as blood sampling procedures indicated. The result was unequivocal; the pressor response to norepinephrine, epinephrine, and angiotensin was regularly accompanied by a fall in electrode potential indicating a fall in sodium concentration, or more precisely, sodium activity. In terms of degree of change, time course, and duration of effect, each agent produced its own characteristic pattern. The depressor response to acetylcholine, histamine and isoproterenol was accompanied by oscillations in the tracing which tended to be inverse to those observed with pressor agents. Later, in a similar arrangement using two electrodes,[17] norepinephrine was shown to produce a rise in potassium inverse to the fall in sodium (Fig. 6).

The technic for electrode monitoring of sodium and potassium in flowing blood was then modified by the method of Haddy so as to control flow rate through the electrode as well as through the vasculature of the limb.[18] The femoral artery of the dog was interrupted by a length of polyethylene tubing fed through a Sigmamotor pump. The femoral vein was similarly lengthened and passed through a smaller division of the pump. The venous outflow passed through sodium and potassium cannula electrodes in a shielded enclosure. This arrangement ensured not only a constant limb inflow but also the passing of a proportion of the venous outflow at a constant rate past the electrodes. Quantitative measurements could also be made because calibrating solutions could be injected into the venous tubing proximal to the pump. One pressure transducer was inserted on the arterial side between pump and limb and another into a brachial artery. Small amounts of vasoactive agents sufficient only to activate the limb vasculature without producing any noticeable systemic effects were used.

In general, limb vasoconstriction induced by norepinephrine or epinephrine was associated with a fall in blood sodium activity and often with a rise of potassium activity (Fig. 7). Larger doses tended to produce a biphasic

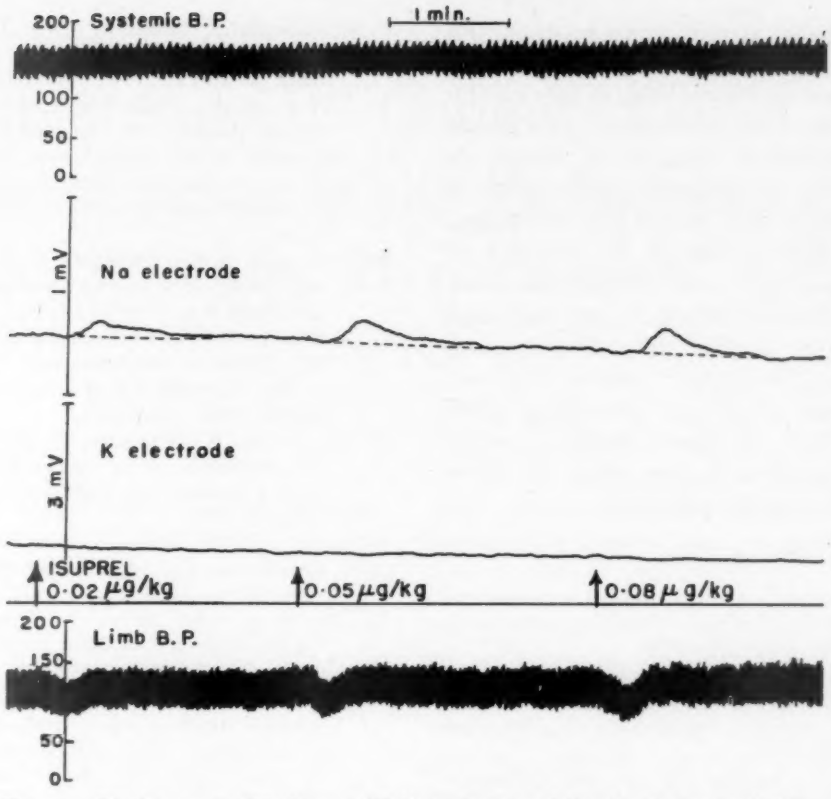


FIG. 9. Limb venous (Na^+) and (K^+) in the dog following intraarterial isopropylnorepinephrine (isoproterenol). Controlled arterial inflow and outflow rates. FROM: JAMIESON, J. D. and FRIEDMAN, S. M. *Circulation Res.* In press.[18]

response in sodium activity, that is, an initial transient rise preceding the fall. Vasoconstriction produced by serotonin or angiotensin was associated with similar sodium activity change unaccompanied by any consistent potassium deflection (Fig. 8). Vasoconstriction produced by Pitressin was associated with a fall in sodium activity and consistent rise in potassium, both noticeably greater in degree and duration than with other agents producing an equal degree of vasoconstriction. Limb vasodilatation induced by isoproterenol, acetylcholine or histamine was accompanied by a rise in blood sodium activity without any consistent change in potassium (Fig. 9).

A full analysis of rates and relations of ion and water movement is clearly required. For the moment, we may conclude that the movements of sodium and potassium associated with changes in blood pressure reflect changes in tension in the peripheral blood vessels.

Only one report disturbs the general consistency of this phase of the investigation. Headings, Bohr and Rondell[19] found that dog carotid artery rings stimulated electrically gained sodium and lost potassium. Epinephrine, however, in an amount sufficient to produce the same contractile response did not produce these changes.

CONCLUSIONS

We may conclude that, in general, an acute increase in tension of vascular smooth muscle is associated with a gain in Na_i and a gain in water. There is a strong suggestion that in some instances at least the gain in water may overshadow the gain in sodium and may also anticipate it. A loss in potassium from cells to environment is almost always observed. Similar ionic exchanges have been observed both in taenia coli and uterus during activity.[20,21]

These experiments give no information regarding the time relations connecting these phenomena nor do they suggest which event is cause and which is effect. They are precisely the changes that would be anticipated if changes in vascular smooth muscle tension involve surging changes of ions across the cell membrane in accord with general ionic theory.

SUMMARY

Experiments dealing with the effects of rapidly acting vasoactive agents on the distribution of sodium and potassium have been ex-

amined in relation to the concept that the tension of vascular smooth muscle is governed by the distribution and mobilities of ions on the two sides of the cell membrane. Evidence derived from chemical analysis of serum or plasma, from the continuous monitoring of blood with sodium and potassium electrodes, and from the direct analysis of samples of vascular wall indicates with reasonable consistency that vasoconstriction is accompanied by a surge of sodium into the cell while potassium usually, but not invariably, moves outward. Converse changes occur in association with vasodilation. These changes would be expected if vascular smooth muscle, like other excitable tissues, is subject to ionic regulation.

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Possible Role of Chronic Excess Salt Consumption in the Pathogenesis of Essential Hypertension*

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DURING THE early seventeenth century Robert Burton in a disquisition on the dietary causes of "melancholy" wrote in his classic book *The Anatomy of Melancholy:* "Common experience finds salt, and salt meats, to be great procurers of this disease, and for that cause, belike, those Egyptian priests abstained from salt, even so much as in their bread, . . . that their souls might be free from perturbations." I will not attempt to relate Burton's statement to hypertension but relative to my thesis it may indicate that the potential hazard of adding excess salt to food has been recognized for thousands of years.

While the fact that Egyptian priests sometimes foreswore the addition of salt to food may indicate the antiquity of this dietary practice, there is very little doubt that until relatively modern times salt was neither cheap nor readily available as a condiment. In most societies of today, by contrast, the addition of salt to food is the rule for both man and child. Despite this widespread usage professional nutritionists have evinced surprisingly little interest in the salt-eating habits of modern man.

During the present century there has been evidence accumulating which suggests a possible relationship between excess salt ingestion and human hypertension. It is this thesis to which I have addressed my efforts in this paper as well as others.[1–13]

NORMAL SALT REQUIREMENTS

It is self-evident that in order to stay in salt (i.e., sodium chloride) balance the organisms must maintain salt intake at a level roughly equivalent to salt loss. But, just as the water level in a tank can remain stationary with either high inflow–outflow or low inflow–outflow, so can salt balance be maintained on high or low intakes.

There is no question that some salt is required by man. However, the available evidence indicates that, at most, the daily requirement is only a few grams for normal subjects who are given a week or two for appropriate physiologic adaptive mechanisms to become operative. It is well established for instance that for untold generations no salt was added to food by numerous vigorous peoples including such diverse groups as Eskimos and certain Chinese, and American Indian and African tribes. Calculations based on the analyzed diets or the known (and relatively constant) sodium content of foods indicate that daily salt intake rarely could exceed 4 or 5 gm. without the addition of salt to food by man and some of the primitive groups probably were actually averaging about 1 gm. per day.[6] Areas in which drinking water has a high saline content constitute a notable exception to the 4 to 5 gm. limit described.

Since the original work of Allen and Sherrill[14] nearly 40 years ago, there have been a number of careful metabolic studies, all of which are in agreement that in people with normal renal function, salt balance can be maintained on daily intakes of less than 1 gm. Our group, [6,7,9,11,15–18] for instance, has studied more than 150 adults whose salt intakes were known (by daily 24 hour urine sodium measurements) to have been limited to 100 to 375 mg. per day for periods ranging from 6 weeks up to almost 5 years. Under ordinary circumstances the mechanisms for reducing salt loss via skin and urine are so effective that continuous intakes of only

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TABLE I
Average Daily Salt Intake (Based on 24 Hour Urine Excretion) in Several Societies

Group	Year	Sex	Salt Intake	
			Average (gm./day)	Range (gm./day)
Alaskan Eskimo	1958, 1960	Both	4	1–10
Marshall Islander (Pacific Ocean)	1958	Both	7	1.5–13
United States (Brookhaven)	1954–1956	Male	10	4–24
Japan				
Hiroshima (South Japan)	1958	Male	14	4–29
Akita (North Japan)	1954	Both	26	5–55

FROM: DAHL, L. K. In: Essential Hypertension. An International Symposium. Berlin, 1960. Springer-Verlag.

1 or 2 gm. daily are more than adequate for metabolic needs, including periods of growth.

AVERAGE SALT INTAKES

It is not easy to obtain actual measurements, as contrasted with the gross estimates, of salt consumption. During the last 10 years my associates and I have been using the 24 hour urinary excretion of sodium as an index of *minimal* sodium chloride intake. Under ideal conditions on a metabolic ward, this is a highly accurate reflection of salt intake but in the field it may be less accurate due chiefly to variable losses through the skin, failure to collect all specimens, and day-to-day fluctuations in intake. Nonetheless, our experience in five different areas of the world indicates that this method is an excellent index of average salt consumption by a group and of *minimal* consumption by person. Similar problems have existed for determining the exact consumption of such things as fats, alcohol or cigarettes, despite which highly useful estimates have been derived.

By use of such technic my associates and I obtained the data summarized in Table I on Alaskan Eskimos, Marshall Islanders, Northern American men and southern Japanese farmers. The studies in northern Japan were made by T. Fukuda of Chiba University.[19] The group averages ranged from a low of 4 gm. per day among the Eskimos to 26 gm. per day among the northern Japanese. In all instances the use of median values rather than averages would not have changed the results significantly. These averages would be misleading if it were assumed that all subjects in a group were consuming the same amount of salt. The variation in the *range* among members of any one group indicates that some subjects may habitually eat little salt while others consume large amounts. However, except for some of the Eskimos and Marshall Islanders, comparison of the data in Table I with the earlier estimates of actual need indicates a considerable excess of intake over normal requirements from which it seems safe to assume that salt intake has no necessary relation to salt requirement.

It is pertinent to question whether an average difference of only a few grams of salt per day could be significant. It is critical to be aware of the fact that "grams per day" defines a *rate* as opposed to a *quantity*. The fable of the tortoise and the hare aptly illustrates that modest rate differentials, operating over long periods of time, can result in striking disparities in end result.

In our laboratory we have studied the effect of variations in average salt intake on Na^{22} turnover, as an index of the rate at which sodium is moving through the body. With daily salt intake of 5 gm. the rate is twice as great as when a patient is taking only 2 gm.; with intakes of 30 gm. the rate is ten times faster than on 2 gm. We suspect that these imposed rate differentials are important physiologically.

SALT APPETITE

In any discussion of salt intake the question of an appetite for salt inevitably arises. There can be no question that salt appetites exist but the question is whether they are acquired or innate. It has been observed[20,21] that primitive Bolivian Indians and Eskimos, who normally added no salt to food, disliked the taste of it initially but could grow to like it quickly. My own children, reared without salt, had no apparent appetite for it until it was induced by their friends. Our patients, reduced to daily intakes of well below 0.5 gm. for months or years, had no salt-craving. Indeed, in such subjects the addition of 1 gm. of salt to their daily intake was cause for comment whereas the addition of 5 or 10 gm. had gone unnoticed when the same patients were ingesting from 10 to

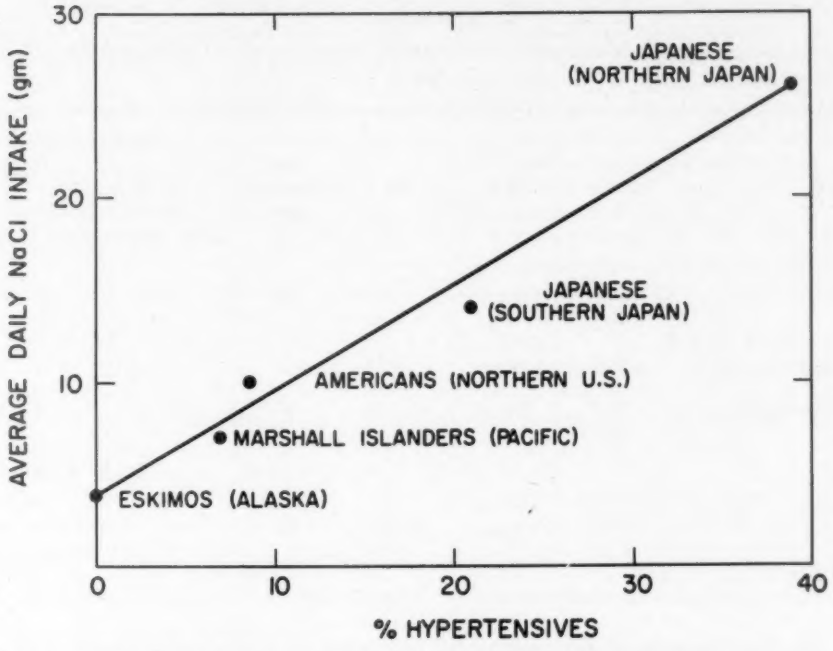


FIG. 1. Correlation of average daily salt (NaCl) intakes with prevalence of hypertension in different geographic areas and among different races. FROM: DAHL, L. K. In: Essential Hypertension. An International Symposium. Berlin, 1960. Springer-Verlag.

20 gm. per day. From these experiences, we have concluded that salt appetite is acquired and therefore warrants no serious consideration relative to being a useful index of salt *requirement*.

EVIDENCE THAT SALT INGESTION MAY BE RELATED TO HYPERTENSION IN MAN

My present discussion will omit hypertension induced experimentally in animals by excess salt consumption since this is the subject of other papers in this seminar.

Our original interest in the relationship of salt to human hypertension was induced by metabolic studies[15–18] which clearly indicated that drastic sodium restriction led to a significant fall in blood pressure in about one-quarter to one-third of patients with essential hypertension. We were further intrigued by observations which suggested that hypertension was relatively uncommon among societies which did not add salt to their food. This suggested the opposite possibility; namely, among groups in which salt was usually added to food the prevalence of hypertension would be frequent and that the larger the average salt intake, the higher the prevalence of hypertension.

Preliminary to more elaborate and time-consuming epidemiologic surveys, a pilot study[5] was carried out at Brookhaven National Laboratory which was highly suggestive of a correlation between salt consumption and hypertension: subjects who were classified as having been on *low* salt intakes throughout their lives had significantly less hypertension (p less than 0.01) and those classified as having been on high intakes had significantly more hypertension (p less than 0.02) than would have been predicted by chance alone.

With these preliminary results in hand we began exploring salt intakes among populations in which the prevalence of hypertension varied. This was done by making sequential 24 hour urine collections for sodium and often by 1 or 2 day collections of the subject's diet as well. The results of these surveys were summarized earlier in Table I. In Table II we have extended these data to include information gathered simultaneously on the prevalence of hypertension in the same subjects. In Figure 1 the data from Table II have been graphed and it is apparent that there is a high degree of correlation between average levels of salt intake and prevalence of hypertension: specifically, the data presently at hand indicate that as daily average salt consumption increases the prevalence of hypertension increases. This graph closely resembles one derived from animal experience by Meneely and his associates.[22] In that study, a colony of rats was divided into groups with the members of each group being chronically fed different levels

TABLE II

Salt Intake (Measured by Urinary Salt Excretion) Compared with Prevalence of Hypertension in Five Geographic Areas

Group	Year	Sex	No.	Age (average)	Salt Intake		% Hypertension (140/90 or over)
					Average (gm./day)	Range (gm./day)	
Alaskan Eskimo	1958, 1960	Both	20	38	4	1–10	0
Marshall Islanders (Pacific)	1958	Both	231	41	7	1.5–13	6.9
United States (Brookhaven)	1954–1956	Male	1,124	36	10	4–24	8.6
Japan							
Hiroshima (South Japan)	1958	Male	456	43	14	4–29	21
Akita (North Japan)	1954	Both	5,301	45	26	5–55	39*

* Systolic and diastolic pressures reported separately. This number (39 per cent) based on diastolic pressure of 90 mm. Hg or more.

FROM: DAHL, L. K. In: Essential Hypertension. An International Symposium. Berlin, 1960. Springer-Verlag.

of sodium chloride; as the average salt consumption of a group increased, so did the mean blood pressure. We recognize that the number of Eskimos included in the present survey is small and it is being extended; however, it is becoming increasingly difficult to find Eskimos sufficiently isolated from civilization to maintain all, or even most, of their ancient food customs.

Individual Variations in Susceptibility to Hypertension: The preceding data correlating increasing average salt intake with increasing prevalence of hypertension are to be used as indicating the *group* probability of the development of hypertension: all *subjects* who consumed the same amount of salt would not have the same probability of the development of hypertension because of variations in individual biological responsiveness.

There is a good deal of evidence which indicates that hereditary factors operate in hypertension.[23,24] We are attracted to the possibility that the interaction of hereditary tissue susceptibility with dietary salt is the common means by which "essential" hypertension develops.[2,5,10,13] With this thesis in mind, a wide spectrum of responses might be expected among individual members of a group consuming roughly equivalent amounts of salt. Furthermore, it would seem probable that some individuals consuming relatively large amounts of salt would not have hypertension while the disease would develop in others who ate fairly modest quantities. This variability in noxious effect on *individuals* is recognized for numerous other subtly lethal agents such as ionizing radiation, cigarettes or excess caloric intake. Thus far, however, we have not encountered *groups* which customarily consumed high salt intakes that had a low prevalence of hypertension or *groups* in which low salt intakes were the rule, associated with high prevalence of hypertension.

SUMMARY

There is evidence which suggests that among groups habitually eating salt in amounts well in excess of requirements, hypertension will be common. Furthermore, it seems likely that as the salt excess increases, so will the prevalence of hypertension. It is proposed that this chronic excess consumption of salt may play a primary role in the pathogenesis of hypertension in man. Variations in biological responsiveness will determine which subjects in a group have the disease.

ACKNOWLEDGMENT

I am particularly grateful to Dr. Robert A. Conard, Medical Department, Brookhaven National Laboratory, and Dr. Christine A. Heller, of the Department of Health, Education and Welfare, Arctic Health Research Center, Anchorage, Alaska, for their assistance in procuring urine samples from the Marshall Islanders and Eskimos, respectively. I also wish to thank Mrs. Lorraine Tassinari and Miss Martha Heine for their technical aid.

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Pathogenesis of Experimental Hypertension Induced by Salt*

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IT IS NOW fairly well established that excessive intake of sodium chloride over a period of time may cause hypertension. Sapirstein, Brandt and Drury[1] found that substitution of 2 per cent sodium chloride for drinking water caused elevation of the blood pressure in the rat. Gepts[2] observed lesions of heart and pancreas, including vascular necrosis, in rats on this regimen. Toussaint and associates[3] were unable to obtain hypertension in rats given 2 per cent salt for drinking but did produce hypertensive vascular disease when a supplement of 5 per cent sodium chloride was incorporated into the diet. Meneely et al.[4] reported that sustained hypertension occurred in rats chronically fed diets rich in sodium chloride (from 6 to 8 per cent of the total diet). Severe renal disease of nephrotic type also developed in some animals. Hypertension was obtained in rabbits ingesting excess salt[5] and also in chickens given isotonic or slightly hypertonic saline to drink in place of water.[6] Selye[7] described renal lesions in chicks which drank 0.9 per cent saline instead of water.

Sodium chloride is also an important factor in steroid hypertension, such as that produced by administration of desoxycorticosterone.[8] In this instance the hypertension presumably depends on retention of sodium and this activity of the steroid is aggravated by salt-loading. Both steroid and salt hypertension may well have the same basic pathogenesis, although the combination of steroid and salt load commonly shortens the time required for development of the disease. Morphologically, the vascular, renal and cardiac lesions of salt and steroid hypertension are essentially the same.

Chronic salt hypertension in the rat has also been under study in this laboratory.[9,10] Salt was administered to young adult animals by using a 1 per cent solution of sodium chloride as the drinking fluid instead of water. The pellets used for food also contained about 1 per cent salt. Some animals were subjected to interval sacrifice, although the majority were followed for the rest of their lives and autopsied at the time of death. Rats on this type of regimen gained weight in normal manner for a few months but thereafter were seriously stunted in growth. Life span was significantly shortened, i.e., to a mean of 12 months as compared to a mean expectancy of 24 months for animals on the same pellet regimen but drinking tap water. Chronic hypertension occurred in about 66 per cent of rats drinking 1 per cent saline. From 5 to 8 months elapsed before the onset of high blood pressure. The blood pressure was labile at first, usually remained so for a variable period and eventually, especially toward the latter part of life, became sustained. The hypertension was accompanied by enlargement of the heart, diffuse vascular disease involving arteries and arterioles, and progressive renal disease. Some grade of azotemia developed in most hypertensive rats. Several died in uremia, although the usual cause of death was pneumonia accompanied by renal dysfunction.

COMPARISON OF EXPERIMENTAL AND HUMAN HYPERTENSION

From the standpoint that organic disease develops in the heart, blood vessels and kidneys, salt hypertension in the rat clearly resembles essential hypertension in man. However, the type of morphologic damage in the blood vessels and kidneys is not identical in the two species. For example, the hypertensive vascular lesion in the rat is necrotizing and is often associated with proliferative or exudative components or both, thus resembling poly-

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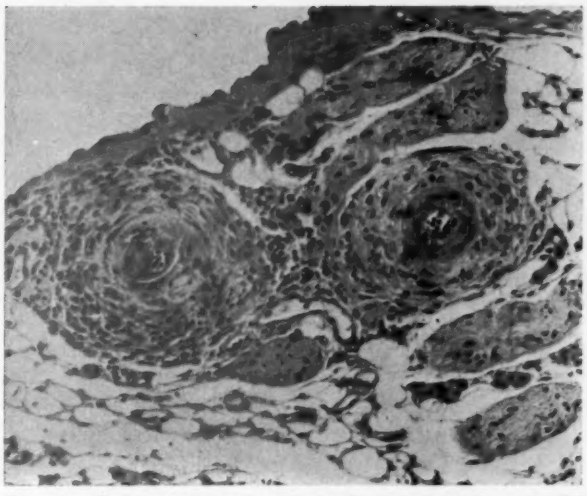


FIG. 1. Polyarteritis of mesenteric arterioles in rat with salt hypertension. (Hematoxylin and eosin; original magnification, ×180.)

arteritis (Fig. 1). This contrasts with the pure fibrinoid necrosis of vessels in malignant hypertension of human subjects. Hence some doubt could be expressed that the vascular lesions in rat and human hypertension are comparable, especially because polyarteritis is often regarded as indicative of the hypersensitive state. However, there seems to be no evidence at present that the polyarteritis in rats with salt hypertension has an immunoallergic or infectious basis. Perhaps this type of lesion in the rat represents a peculiarity in species response. Even though morphologically different, it is quite possible that the polyarteritis of hypertension in the rat and the fibrinoid necrosis of malignant hypertension in the human being have a similar etiology.

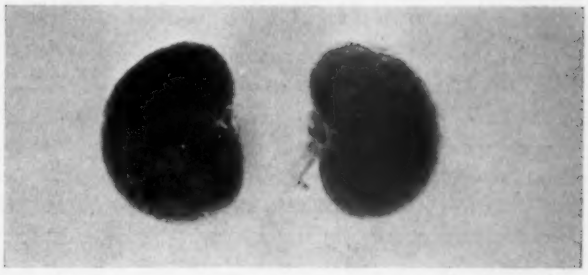


FIG. 2. Symmetrically granular kidneys in rat with salt hypertension.

In rats with salt hypertension, the kidneys show a symmetric bilateral lesion characterized by uniform granularity of the outer surfaces; the gross appearance is comparable to human nephrosclerosis (Fig. 2). However, microscopically the intrarenal vascular changes are also of polyarteritic type and in addition there generally is diffuse glomerular disease with necrotizing, degenerative and proliferative components such as one would tend to associate with glomerulonephritis (Fig. 3). This is in contrast to the relatively inconspicuous glomerular damage in human benign nephrosclerosis, but resembles the widespread and sometimes severe glomerular lesions of malignant nephrosclerosis. The etiology of the glomerular disease is not established for either rat or man, although an immunoallergic or infectious basis seems unlikely on the basis of present evidence. Again, the possibility that rat nephrosclerosis

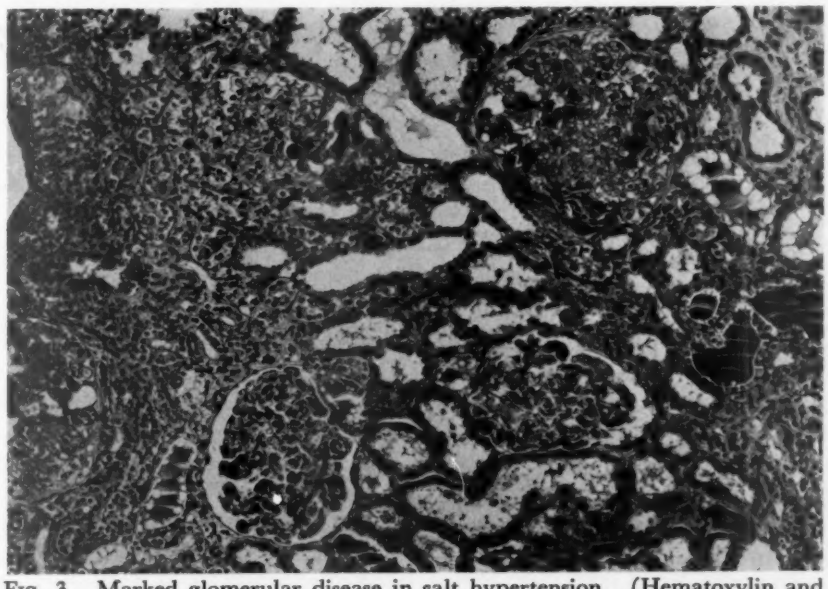


FIG. 3. Marked glomerular disease in salt hypertension. (Hematoxylin and eosin; original magnification, ×150.)

TABLE I
Renal Ablation and Salt

Ablation (%)	Incidence of Lesions (%)		
	High Blood Pressure	Blood Vessels	Kidney
0	66	60	40
50	94	83	74
75	100	100	90

TABLE II
Renal Ablation in Animals on Salt

Ablation (%)	Hypertension	
	%	Onset
0	66	8 months
50	94	4 months
75	100	2 weeks

and human malignant nephrosclerosis may have a common origin, or an origin in common, merits some consideration. How far one can go at present in comparing rat nephrosclerosis with human benign nephrosclerosis is not clear.

Synergistic Effect of Reduced Renal Mass and Salt Load

The hypertensive activity of salt is substantially enhanced by reduction in renal mass.[10,11] There is also marked synergism as regards the induction of vascular disease and nephrosclerosis. With progressive renal ablation salt induces these lesions more rapidly and with greater frequency and severity. Thus with both kidneys intact chronic salt ingestion yielded hypertension in 66 per cent of animals, vascular disease in 60 per cent and nephrosclerosis in 40 per cent. In unilateral nephrectomized rats the same dietary regimen gave high blood pressure in 94 per cent of animals, while vascular disease and nephrosclerosis occurred in 83 and 74 per cent, respectively. However, with three-fourths of renal mass removed the incidence of hypertension and vascular disease was 100 per cent and of nephrosclerosis 90 per cent (Table I). The smaller the kidney stump the more rapid and severe is the injury from salt. The latter will often yield fulminant nephrosclerosis within a few weeks in three-fourths ablated rats as against an interval of several months for animals with both kidneys present (Table II). Rats with 75 per cent nephrectomy and on a high salt regimen usually become hypertensive within 1 or 2 weeks as compared to from 5 to 8 months for animals with intact kidneys.

A clear explanation for the synergism of reduced renal mass and salt load is not available. One possibility rests on the thesis that an adequate amount of normal renal tissue is required to maintain the structural integrity of the peripheral vascular bed and also to supply a substance which regulates vascular tone.[12,13] Perhaps the salt in some way suppresses the production or activity, or both, of antihypertensive material derived from the kidney stump. It seems less likely that salt acts through a renal pressor mechanism, although this is not excluded with certainty. There is insufficient evidence that organic renal disease plays a role in the origin of salt hypertension. Rats with chronic salt hypertension often show severe renal disease, but at the onset of hypertension and often during its early stage, kidney lesions are minimal or relatively slight, at least by conventional methods. Another possible mechanism is that significant reduction in the number of functioning nephrons has an adverse effect on renal management of electrolytes and hence on electrolyte distribution and composition in the tissues of the body. In the case of a salt load, retention of sodium and water might be augmented and the electrolyte state of the peripheral vascular bed altered so as to enhance tonus of the blood vessels.

Sequence of Vascular Events in Salt-Induced Hypertension

Interval sacrifice of animals suggests a certain sequence of events in the development of hypertensive vascular disease as induced by salt.[10] Peripheral blood vessels appear to be injured first and the initial effect is the functional one of increased vascular tone. The latter causes high blood pressure which would thus represent a very early sign, perhaps the earliest, of the widespread involvement of peripheral vessels. At the time of initiation of the hypertension the blood vessels, when studied by conventional histologic technics, often show sparse and relatively slight disease or are morphologically unaltered. Subsequently, however, the high blood pressure is accompanied by

progressive organic damage to arteries and arterioles, widely distributed in the body and including such sites as pancreas, mesentery, adrenals, gastrointestinal tract and kidneys. The renal lesions develop more or less simultaneously with those of other peripheral vessels, and we prefer to interpret them as the renal component of the generalized vascular disease.

Thus the usual sequence in salt-induced hypertensive vascular disease seems to be as follows: (1) increased peripheral vascular tone, (2) hypertension, (3) generalized vascular disease, and (4) renal disease (nephrosclerosis). The precise manner in which the vascular lesions arise is not clear, although some investigators have regarded them as a consequence of the high blood pressure itself. At present we feel that the evidence which has been cited in favor of this origin is inconclusive. At the least hypertension is not a *sine qua non* for the vascular disease. As with hypertension, it seems unlikely that the vascular lesions which result from salt-loading are of renal origin, i.e., elaboration of a necrotizing agent or loss of a protective agent. The excess salt may be directly responsible for the lesions, perhaps by initiating ionic imbalances in the walls of the blood vessels. Such a mechanism could apply to both the functional (increased tone) and organic aspects of the injurious process. However, the sometime delay in appearance of the morphologic damage, and also its complete dissociation from high blood pressure in certain instances, suggest somewhat different or additional requisites for this component. That an altered electrolyte status is apparently capable of inducing significant tissue lesions is shown by the development of myocardial necrosis in rats with potassium deficiency[14,15,16] and also in rats on an electrolyte-steroid regimen.[17]

Arterial Wall Sodium Content in Hypertension

Several concepts have been offered to explain how an altered pattern of sodium in the vessel wall might lead to increase in vascular tone. For example, enhanced neuromuscular parasympathetic transmission and hence vasoconstriction may arise from increased sodium content.[18] Another possibility is that decrease in the gradient between extracellular and intracellular sodium in the muscular coat of the arteriole produces vasoconstriction.[19] There is also the concept that vascular edema resulting from accumulation of sodium and water reduces the diameter of the vessel wall sufficiently to lead to increased resistance.[20]

Renal Hypertension: Many studies have been made on the electrolyte composition of various tissues, including blood vessels (principally aorta), in experimental hypertension. The results have not been uniform and differences of opinion existing regarding the significance of the data. In Grollman's study[21] no significant change from the normal was observed in electrolyte composition of various organs of rats rendered hypertensive through choline deficiency diet.[21] Ledingham[22] noted no important changes in either intracellular sodium or potassium in the hearts of rats with acute renal hypertension. He believed that the increase in total sodium content was explained by expansion of extracellular fluid. Tobian and Binion[23] reported an increase in sodium and potassium content of the aorta in hypertensive rats and part of the sodium increase was due to intracellular accumulation. Increased content of potassium in the aorta rather than sodium has been stressed as the significant change.[24–26] Daniel and Dawkins[26] reported an elevation in potassium concentration within the aorta in early but not in chronic hypertension. Greene and Sapirstein[27] noted a substantial rise in the total body sodium of rats with renal hypertension and believed that this could not be explained by expansion of extracellular volume. They postulated either deposition of sodium in bone or an increased amount of sodium in intracellular position.

Salt-Induced Hypertension: We have also explored this area in the rat using the mesenteric arterial bed for analysis. This site was selected because the mesenteric arteries and their branches are a frequent and relatively early site for development of the typical vascular lesions observed in hypertension. The vascular disease is identical with that which occurs in small arteries and arterioles throughout the body, therefore, electrolyte alterations here are likely to be representative of the peripheral vascular bed. Of especial interest were the changes which occurred in these vessels prior to the development of recognizable organic disease, and also prior to or concomitant with the development of hypertension. The latter item might tend to exclude high blood pressure itself as the cause of any changes.

The mesenteric arteries of rats fed excess salt[28] showed changes in electrolyte composition similar to those observed in the early stage

of renal hypertension.[29] There was a statistically significant elevation in the content of total sodium and of potassium, as well as in chloride and water. Sodium plus potassium content (combined cation values were derived from the mean of sums of sodium and potassium concentration for each rat) was also increased, although the combined cations showed no increase over the normal in terms of concentration of water in tissue. Values for extracellular sodium obtained by using chloride space as a measure of extracellular fluid indicated that extracellular sodium accounted for only part of the total rise of this cation and hence that the intracellular phase contained more sodium. However, there is some doubt that chloride space is an adequate measure of extracellular volume in the mesenteric arterial bed.

Our data on electrolyte composition of the mesenteric vascular bed in rat hypertension are in accord with previous findings in the aorta as obtained by some investigators and are contrary to the results of others. The mesenteric arteries of both hypertensive and normal rats showed considerable variation in both sodium and water content, indicating that the latter constitute a labile system in this location. This did not apply to potassium values. Elsewhere, as in the heart and skeletal muscle, the content of sodium and water seemed considerably more stable.

It is of interest that a common pattern of electrolyte alteration in the vascular bed characterizes high blood pressure in the rat whether the hypertension is induced by salt or by renal injury, that the chemical changes may antedate the hypertension, and that in case of salt the chemical changes in the vessels cannot be readily attributed to renal dysfunction. Thus, while at present the significance of intravascular electrolyte disturbances is far from clarified, the possibility remains that such disturbances may play a role in the genesis of rat hypertension.

Summary

1. Chronic salt ingestion in the rat often yields hypertensive cardiovascular renal disease.

2. The natural history of this disease resembles that of essential hypertension in man. Morphologically, however, neither the vascular lesions nor the renal disease which accompany hypertension in the two species are strictly comparable.

3. In the rat, salt loading and renal ablation are synergistic in producing hypertensive vascular disease. The reason for this is not clear, although it may relate to defective sodium metabolism.

4. Altered electrolyte status in the peripheral vascular bed may play a role in the genesis of rat hypertension.

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Hypertension and Renal Cardiovascular Pathology in Adrenalectomized Salt-Loaded Rats*

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CONNECTIONS BETWEEN the function of the adrenal cortex and some diseases such as hypertension, diabetes and nephrosclerosis have been suspected ever since the association between adrenal cortical tumors and the symptoms of Cushing's disease was noted. Some patients with Cushing's disease have hypertension and some have diabetes. More recently it has been observed that some patients with primary aldosteronism are hypertensive. All the reasons for postulating a relationship between adrenal cortical function and disease were brought into focus by Selye's concept of the "adaptation diseases" in which a derailment of adrenal cortical function during exposure to nonspecific stress was assigned a key role in the etiology of many diseases.[1]

The experimental basis for the concept of the adaptation diseases was the pathologic findings obtained in rats overdosed with steroids. Hypertension and renal and cardiovascular damage occurring in rats overdosed with corticoids are most severe when one kidney has been removed and the animal is given a high intake of sodium chloride. Selye describes the corticoids as the primary cause of the pathology and characterized uninephrectomy and high salt load as conditioning factors. Investigators agree with the results of these basic experiments, but there is disagreement as to the relative importance of the individual factors that make up the causal pattern for these experimentally induced diseases. We are interested in the proposition that the primary cause of such pathology is the excess sodium chloride, which is more toxic when the renal mass is reduced by uninephrectomy and when sodium-retaining steroids are administered. The reasons for the assumption of the primary pathogenic nature of excess sodium chloride are as follows: (1) When the sodium chloride intake of desoxycorticosterone acetate-overdosed rats is restricted to a level just adequate to meet nutritional requirements, the administration of steroid does not cause nephrosclerosis, cardiovascular pathology or hypertension.[2] (2) Meneely et al.[3] found that high salt loads cause hypertension and renal and cardiovascular pathology even when both kidneys of the experimental animals are intact. (3) Crane, Wilgram and Ingle[4] have shown that the processes leading to hypertensive vascular disease do progress—although slowly—in adrenalectomized rats without hormonal therapy. (4) Fregly[5] has reported on the elevation of blood pressure in the adrenalectomized rat given high loads of sodium chloride without hormonal therapy.

The experiments reported here are an extension of the work mentioned previously. Crane and Ingle[6] have demonstrated that the untreated adrenalectomized rat rids itself of the high salt load with less water than do similar animals with intact adrenal glands. In other words, it loses more salt on the same water intake than intact rats. Therefore, less salt is retained in adrenalectomized rats. Nevertheless, as will be shown in this report, the salt-loading of adrenalectomized, uninephrectomized rats does indeed lead to hypertension and cardiovascular pathology after 6 months to 1 year. We therefore present the thesis that in Selye's experiments the primary pathogenic

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TABLE I
Six Months Experiment—Group 1
(Control Rats)

Rat No.	Body Weight (gm.)		Organ Weight (mg.)					Pathology (0 to 5)*			Blood Pressure (mm. Hg)
								Kidney		Heart	
	Initial	Final	Heart	Kidney	Thymus	Spleen	Adrenal	Gross	Micro.		
1	300	491	1,260	1,500	276	640	21	0.0	1.5	0	120
2	300	513	1,240	1,290	202	670	21	0.0	1.5	0	120
3	300	511	1,330	1,500	386	780	22	0.0	0	0.25	110
4	300	535	1,410	1,620	292	560	26	0.0	1	0	126
5	300	523	1,350	1,510	184	780	24	0.0	0.5	0	118
6	300	496	1,365	1,480	264	670	25	0.0	0.5	0	120
7	300	524	1,320	1,435	176	800	25	0.0	1	0	127
8	300	514	1,300	1,530	362	730	23	0.5	1	0	114
9	300	547	1,400	1,615	125	710	22	0.5	1.5	0	116
10	300	541	1,415	1,580	326	915	29	0.5	2	0	150
11	300	560	1,350	1,600	286	1,050	26	0.5	1.5	0	118
12	300	492	1,220	1,450	268	750	24	0.0	0	0	134
13	300	471	1,260	1,460	264	800	22	0.0	1	0	120
14	300	451	1,150	1,520	438	770	25	0.0	0.5	0.25	116
Average	300	510	1,312	1,506	276	758	23.9	0.14	0.96	...	122

* In this and all other tables, the grading system used is similar to the one published previously (*Arch. Path.*, 690: 68, 1959). Although the experimental conditions were different, the morphologic criteria allowed adherence to the same type of grading system.

factor is the high dietary salt load, which is secondarily aggravated by salt retention due to overdosing with corticoids.

METHODS

Rats of the Sprague-Dawley strain were maintained on Rockland rat pellets until they became adult. They were then given a medium carbohydrate diet to eat *ad libitum*. When sodium chloride was added to the diet, it was expressed as per cent of dry mix before water was added. The animals were adapted to a salt load by increasing the amount of sodium chloride by 1 per cent per week until the desired load was reached. The animals were kept in individual cages at room temperature (74–78°F.). Uninephrectomy and adrenalectomy were then performed. The adrenals were removed with the capsule intact and with as much of the pedicle and surrounding fat as possible. Immediately following operation, each rat was given 5,000 units of penicillin and 5 mg. of streptomycin. This was not continued. No cortical hormone was given in any of the experiments reported here. At the completion of the experiments, blood pressure was determined under ether anesthesia by direct cannulation of the abdominal aorta. The cannula was attached to a mercury manometer by means of a short length of fine bore rubber tubing filled with heparinized saline. The pressure was recorded when the anesthesia first became light enough to permit slight retraction of the rat's hind foot when the toes were pinched.

Following the determination of blood pressure, the rat was exsanguinated, autopsy was performed and gross pathologic changes were noted. The heart, kidney and mesentery were removed, fixed in 10 per cent calcium formalin, and, after being processed in paraffin, were stained with hematoxylin and eosin.

EXPERIMENTS AND RESULTS

Two sets of animals, one on the diet for 6 months, the other for 1 year, were used.

SET A—SIX MONTHS EXPERIMENT

Group 1: Fourteen intact male animals ate chow (Rockland) *ad libitum* after reaching a weight of 300 gm. The blood pressure was normal (Table I), averaging 122 mm. Hg. The microscopy of heart and kidneys was consistent with findings obtained in normal rats of that age group.

Group 2: Eight male adrenalectomized, uninephrectomized rats ate *ad libitum* a medium carbohydrate diet with 4 per cent added salt. Their blood pressure was significantly elevated (Table II), compared with normal control

TABLE II

Rat No.	Body Weight (gm.)		Organ Weights (mg.)			Pathology (0 to 5)					Aorta Micro.	Mesentery		Blood Pressure (mm. Hg)
						Kidney			Heart					
	Initial	Final	Kidney	Heart	Thymus	Gross	Parenchyma	Vessels	Parenchyma	Vessels		Gross	Micro.	
A. Six Months Experiment—Group 2 (4 per cent added salt; male adrenalectomized, uninephrectomized rats)														
38	287	580	4,480	1,920	278	4.0	3.5	1.0	0.0	0.5	0.0	0.0	0.0	160
39	283	586	2,635	1,645	255	4.0	2.5	0.5	0.0	0.5	0.25	0.0	0.0	142
41	261	446	2,060	1,460	264	3.5	1.5	0.5	0.0	1.0	0.0	0.0	1.0	126
44	256	424	1,755	1,460	250	1.0	1.0	1.5	0.0	0.0	0.0	0.0	0.25	132
47	243	538	3,440	1,730	202	5.0	2.5	0.5	0.0	0.5	0.0	0.0	0.0	154
50	300	410	1,945	1,390	251	3.0	1.5	1.0	0.0	1.0	0.0	0.0	0.0	136
53	285	550	2,750	1,435	311	4.5	2.5	0.5	0.0	0.5	0.25	0.0	0.0	132
56	279	420	1,625	1,500	153	0.5	1.5	1.5	0.0	0.0	0.25	.00	0.0	134
Average	274	494	2,586	1,567	245	3.19	2.06	0.87	0.0	0.5	0.09	0.0	0.16	139.5
B. Six Months Experiment—Group 3 (4 per cent added salt; female adrenalectomized, uninephrectomized rats)														
5	300	442	1,565	1,265	304	1.0	0.5	0.0	0.0	0.0	0.0	0.0	0.0	110
8	271	354	1,475	1,200	205	2.5	1.0	0.5	0.0	0.5	0.0	0.0	0.0	120
14	260	348	1,550	1,225	273	4.0	1.5	0.5	0.0	0.5	0.0	0.0	0.0	132
17	268	329	1,585	1,200	304	0.0	1.0	0.5	0.0	0.0	0.0	0.0	0.0	137
23	259	300	1,360	950	255	1.0	0.5	0.0	0.0	0.0	0.0	0.0	0.0	112
26	250	315	1,370	1,000	178	1.5	1.0	0.5	0.0	0.5	0.0	0.0	0.0	116
29	245	354	1,270	1,265	242	2.5	1.5	0.5	0.5	0.5	0.0	2.5	3.0	142
32	235	374	1,475	1,200	252	1.5	0.5	0.5	0.0	1.0	0.25	0.0	0.0	130
35	266	379	1,660	1,175	238	2.5	1.0	0.5	1.0	0.5	0.0	0.0	0.0	112
Average	262	355	1,479	1,167	250	1.83	0.94	0.44	0.17	0.50	0.03	0.28	0.33	123

rats of the same age. Heart weights increased. They lost weight. There was some damage to the parenchyma of the kidney as illustrated by cast formation and tubular degeneration. The glomerular apparatus was mildly involved in four of the eight animals.

Group 3: Nine female adrenalectomized, uninephrectomized rats ate *ad libitum* the medium carbohydrate diet with 4 per cent added salt. As can be seen from Table IIB, 4 per cent salt did not bring about any severe pathology after 6 months in female adrenalectomized rats.

Group 4: Five male adrenalectomized, uninephrectomized rats ate the medium carbohydrate diet *ad libitum* with 12 per cent added salt for 6 months. Table IIIA shows that their blood pressure was markedly elevated. Heart weights were increased. The kidney, upon microscopic examination, showed distinct degenerative changes in the tubules and early inflammatory lesions in the glomerular apparatus. Heart and mesentery had little microscopic pathology.

Group 5: Eighteen female adrenalectomized, uninephrectomized rats ate *ad libitum* the medium carbohydrate diet with 12 per cent added salt for 6 months. Table IIIB shows that their blood pressure was significantly elevated, although not quite as much as in their male counterparts. Hearts, mesentery and aorta did not show any particular microscopic changes but the kidney showed pronounced pathologic lesions in four of eighteen animals. Since Table IIIB presents averages of eighteen rats, the drastic changes in these four animals are somewhat blurred out.

Summary: After 6 months on a 4 per cent salt diet, male adrenalectomized, uninephrectomized rats had mild hypertension and kidney damage, more visible in the tubular part than in the glomeruli. Male rats on a 12 per cent salt diet exhibited more advanced pathology and more severe hypertension. Female rats were less affected by both the 4 and 12 per cent added salt.

SET B—ONE YEAR EXPERIMENT

Group 1: Twelve normal rats ate *ad libitum* a stock Rockland diet without added salt.

TABLE III

Rat No.	Body Weight (gm.)		Organ Weight (mg.)			Pathology (0 to 5)			Blood Pressure (mm. Hg)
						Kidney		Heart	
	Initial	Final	Kidney	Heart	Thymus	Gross	Micro.	Micro.	
A. Six Months Experiment—Group 4 (12 per cent added salt, male adrenalectomized, uninephrectomized rats)									
37	292	490	3,310	1,740	284	3.5	2.0	1.5	174
40	264	523	3,445	1,995	299	5.0	3.0	1.0	166
42	259	380	1,895	1,325	167	2.0	2.5	1.0	132
55	286	412	2,215	1,400	264	3.0	1.0	0.5	156
60	265	406	2,225	1,355	284	2.0	2.5	0.5	126
Average	273	442	2,618	1,563	260	3.10	2.5	0.90	151

B. Six Months Experiment—Group 5 (12 per cent added salt, female adrenalectomized, uninephrectomized rats)

Rat No.	Body Weight (gm.)		Organ Weights (mg.)			Pathology (0 to 5)					Aorta Micro.	Mesentery		Blood Pressure (mm. Hg.)
						Kidney			Heart					
	Initial	Final	Kidney	Heart	Thymus	Gross	Parenchyma	Vessels	Parenchyma	Vessels		Gross	Micro.	
1	300	373	1,845	1,515	359	2.5	1.0	1.0	0.0	0.0	0.0	0.0	0.0	178
2	287	323	1,955	1,965	269	5.0	2.5	1.0	0.0	0.5	0.0	1.0	3.0	178
3	286	354	1,940	1,300	189	2.5	1.5	1.0	0.0	0.0	0.0	0.0	0.0	160
4	281	353	1,900	1,260	275	3.5	1.5	0.5	0.0	0.5	0.0	0.0	0.0	145
6	278	326	1,735	1,400	208	3.0	1.5	1.0	0.0	0.0	0.25	0.0	0.0	143
7	277	337	1,750	1,200	242	2.5	0.5	1.0	0.0	0.5	1.0	0.0	0.0	132
9	271	338	2,110	1,135	149	4.0	2.5	1.0	0.0	0.5	1.0	0.0	0.0	152
10	268	331	1,895	1,210	182	2.0	1.5	1.0	0.0	0.25	0.0	0.0	0.0	148
12	260	310	1,570	1,180	248	4.0	1.5	0.5	1.0	1.0	1.0	0.0	0.0	173
13	261	343	1,785	1,290	146	2.5	2.0	0.5	0.0	0.5	0.0	0.0	0.0	142
16	258	320	2,000	1,920	304	5.0	4.5	0.5	0.5	1.5	0.0	5.0	5.0	190
22*	250	283	1,640	1,215	187	1.0	0.5	0.5	0.5	1.0	0.0	0.0	0.0	132
24	247	328	1,740	1,360	298	1.5	1.0	0.5	0.5	0.5	0.25	0.0	0.0	152
27	240	303	1,630	1,140	167	2.0	1.0	0.5	0.0	0.5	0.5	0.0	0.0	150
28*	240	268	1,500	1,030	116	1.0	0.5	0.5	0.5	1.0	0.0	0.0	0.0	116
30*	235	281	1,510	1,020	393	2.5	0.5	0.0	0.0	0.5	0.0	0.0	0.0	120
33*	228	297	1,570	995	186	1.5	1.5	0.5	1.0	0.5	0.0	0.0	0.0	120
34	260	311	1,360	1,210	248	1.0	0.5	1.0	0.0	1.0	1.0	0.0	0.0	144
Average	263	321	1,774	1,297	231	2.61	1.44	0.69	0.22	0.42	0.28	0.33	0.44	149

* These four rats together in one cage. Each had large patch of skin eaten away. Rats ate poorly and were skinny. Blood pressure without these four rats = 156.

As can be seen from Table IVA, their blood pressure was within normal limits and few changes could be discerned in their kidneys and hearts: observations entirely compatible with findings obtained in normal rats of that age.

Group 2: Seven male adrenalectomized, uninephrectomized rats, after having reached an initial weight of 300 gm., ate *ad libitum* a medium carbohydrate diet containing 4 per cent extra salt. Table IVB shows that their average blood pressure was markedly elevated. Heart weights were increased considerably. There was some damage to the myocardium as represented by mild interstitial myocarditis in most cases. Damage to the kidneys was striking. Very extensive cast formation and tubular degeneration dominated the microscopic picture. The glomeruli showed thickening of the membrane and loops with partial adherence to the capsule. In some rats the capillary loops of the tuft had become adherent to one another, had retracted and the widened space of Bowman was filled with a protein-rich exudate. In other instances, the inflammatory process in the glomeruli had led to complete obliteration of the tuft. However, only occasionally did the glomeruli exhibit the scarring and hyalinization which is so conspicuous in malignant nephrosclerosis in man, or in salt-loaded rats overdosed with steroids. Apparently these salt-loaded

TABLE IV

No. Rat	Final Body Weight (gm.)	Organ Weights (mg.)					Kidney Pathology (0–5)		Heart Micro.	Blood Pressure (mm. Hg)
		Heart	Kidney	Thymus	Spleen	Adrenal	Gross	Micro.		
A. One Year Experiment—Group 1 (Male control rats)										
1	460	1,050	1,480	28	400	22	1.0	1.5	0	118
2	466	1,125	1,330	198	650	20	0.5	0	0	114
3	478	1,150	1,450	90	560	22	0.5	1	0	120
4	484	1,150	1,400	166	610	24	0.5	0.25	0	132
5	490	1,080	1,350	72	560	24	1.0	1	0.25	130
6	472	1,120	1,280	126	620	26	0.5	1	0	124
7	491	1,210	1,450	40	590	24	0.5	0	0	116
8	458	1,050	1,340	114	580	24	0.5	0	0	116
9	452	1,000	1,355	118	710	26	0.5	0	0	118
10	466	1,150	1,550	120	620	28	0.5	0.5	0.25	120
11	451	1,070	1,400	94	580	26	0.5	1.5	0	134
12	494	1,130	1,440	100	450	28	1.0	0	0	114
Average	471	1,107	1,402	105	577	24.5	0.63	0.56	0	121
B. One Year Experiment—Group 2 (4 per cent added salt, male adrenalectomized, uninephrectomized rats)										
1001	560	1,870	2,790	147	...	...	1.0	2.0	2	172
1002	652	1,950	4,390	69	...	...	4.0	3.0	1	156
1003	515	1,345	2,850	100	...	...	2.5	3.5	1	146
1004	559	1,960	3,595	104	...	...	4.5	3.5	1.5	178
1005	453	1,980	3,775	84	...	...	5.0	4.0	1	154
1006	518	1,985	5,900	120	...	...	5.0	4.0	1	188
Average	517	1,775	3,615	93.8	...	...	3.4	3.1	1.21	165

rats were autopsied before hyalinization of the glomeruli could take place. Likewise, the afferent vessels to the glomeruli were thickened and hypertrophic, which is consistent with the accompanying hypertension; however, arteriolar necrosis was rare.

Summary: Uninephrectomized, adrenalectomized rats eating 4 per cent salt diet for 1 year showed pronounced parenchymatous and vascular changes in the kidneys and a moderate degree of interstitial myocarditis. The changes in the parenchyma of the kidney were more pronounced than the changes in the vessels and in the glomeruli, which did not progress to severe malignant nephrosclerosis.

COMMENTS

When compared with normal rats, adrenalectomized rats consuming 4 per cent salt diet reveal only little damage to the parenchyma of the kidney and a moderate increase in blood pressure, more pronounced in the male than in the female rats. When 12 per cent salt is added to the diet the changes become more marked, again better demonstrable in male than in female rats. The most important group consists of the six male adrenalectomized and uninephrectomized animals that were kept on a 4 per cent salt diet for 1 year. These animals, compared with the control group, had the most marked changes of all the experimental groups. The adrenalectomies in our experimental rats were performed with eare. Experience in this laboratory has shown that rats will not survive on a minimal salt intake after adrenalectomy done with our technic. Only when extra salt is added to the diet do adrenalectomized rats survive. This is taken as evidence that the animals are adrenally insufficient and that whatever accessory adrenal tissue may remain does not produce enough hormones to keep the animals alive on a diet with a minimal salt concentration. It is true that when adrenalectomized rats are maintained on commercial or experimental diets containing 0.5 to 1 per cent sodium chloride,

some animals may survive indefinitely when all other supportive therapy is withdrawn. Such animals may have accessory adrenal cortical tissue, but in our experience they remain hypersensitive to stress and show other signs of chronic adrenal insufficiency. In view of this experience, we interpret the data obtained in these experiments to mean that uninephrectomized and adrenalectomized rats may indeed have signs of early nephrosclerosis and that hypertension may develop. We attribute this to the high dietary salt load. Microscopic parenchymal damage to the kidney is extensive, but damage to the glomerular apparatus is not so severe as that noted after salt loading plus steroid injections. This is not surprising because steroid administration does indeed greatly potentiate salt retention and therefore aggravates the damage produced by salt loading. Since hypertension and early "malignant" nephrosclerosis can be produced in rats in the absence of the adrenal gland, it is concluded that in Selye's model experiments the salt is the primary pathogenic agent. A possible derailment of corticosteroid secretion does not, therefore, appear to be the primary pathogenic factor.

Summary

Male and female adrenalectomized and uninephrectomized rats were kept on diets containing 4 and 12 per cent salt for 6 months and on a diet containing 4 per cent added salt for 1 year. Hypertension, increased heart weight, and microscopic lesions in the kidney consistent with early "malignant" nephrosclerosis were observed in male rats after 6 months on a 12 per cent salt diet, and in male rats after 1 year on a 4 per cent salt diet.

These data reveal that hypertension and early nephrosclerosis can be induced by salt loading in the absence of the adrenal glands. It is also concluded that mineralosteroids of the adrenal cortex are not the primary pathogenic agents in inducing these conditions. It is probable that they merely potentiate the primary damaging effect of a high salt load.

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Panel Discussion

Chairman: Dr. Arthur Grollman

Discussion of Papers by Drs. Friedman and Friedman; Dahl; Koletsky; and Wilgram and Ingle

George Meneely (Nashville, Tenn.): I think there are two kinds of salt hypertension and I will show you in a subsequent presentation that they have quite different electrolyte distributions, depending on whether the rats are eating very high levels of salt or just moderate levels of salt. Only at the very high levels of salt do we see the severe arteriolar disease, which I showed this morning and Dr. Koletsky described this afternoon. The rats eating less salt have what we conceive to be hypertension, but do not seem to have vascular lesions or much of any other kind of lesion.

We think very highly of Dr. Wilgram's work, but we do not agree with his picture at the lower levels of high salt feeding.

I would like to comment on Dr. Dahl's northern Japanese fellow who ate 55 gm. of salt. I made a few calculations, and if I am correct, a Japanese farmer who lives to a ripe old age and eats 55 gm. of salt each day during his life would have his glomeruli filter 277,200 pounds or 138 tons of salt. Somewhere in his backyard there ought to be a two-ton pile of salt!

Question: Why not a 138 ton pile?

George Meneely: It has to do with the amount of glomerular filtrate formed and the amount of urine excreted.

John Weller: This morning I mentioned that we had done an experiment similar to Dr. Koletsky's. We have analyzed aortic and various other tissues.

We agree completely, in that we also found sodium, potassium, chloride and water contents higher in aortas of animals ingesting excess sodium chloride. Our technic differs in that we were using 1.75 per cent and 2 per cent saline drinking water, which, as with removal of the kidney, will promote the increase in blood pressure. In the group of rats receiving 2 per cent NaCl the blood pressure peak was reached at the sixth week, then the blood pressure declined. During this time the weight of the animals decreased too. Usually there is a failure to gain weight, but in these experiments we had actual loss of weight. The tissues, especially skeletal muscle, appeared to be potassium-deficient in this particular group of animals. Superimposed potassium deficiency complicated the electrolyte pattern.

MELVIN FREGLY (Gainesville, Fla.): One thing that has always bothered me about sodium chloride loading is the change in acid-base balance which probably results from long-term treatment. In our salt hypertension studies we supply sodium and chloride in a 1 : 1 ratio. Sodium concentration of the blood plasma is about 140 mEq. and chloride concentration about 110 mEq. per L. This is not a 1 : 1 ratio. By requiring a rat to take a 1 : 1 ratio over a long period of time, something else has to be altered in its internal environment. This may be the bicarbonate ion concentration. I would expect some changes in acid-base balance in long-term salt loading experiments. Has anybody investigated this?

EDWARD RADFORD (Boston, Mass.): We have looked at the effects of acid-base balance from the standpoint of renal regulation and water excretion. We can produce changes in the renal concentrating mechanism, which presumably has something to do with the medullary distribution of sodium, by altering the acid-base balance of the diet. For example, adding lysine-free base (0.16 mM./gm. of Purina dog chow) for 3 weeks lowers maximum urine concentration in young rats. In old rats the acid-base effects are more striking. I will present more of these results later, but with regard to excretion of water in relation to electrolytes, there does seem to be a relationship between acid-base balance and the kidneys.

EDWARD FREIS (Washington, D. C.): Perhaps Dr. Koletsky will discuss the reasons why he thinks that hypertension is not the cause of the vascular damage. It is my impression from reviewing the literature that it probably is. The experiments of Gaunt and others have shown that if the elevation of blood pressure in corticoid and renal hypertensive rats is prevented by antihypertensive drugs, the vascular lesions do not occur. I believe another investigator has mechanically elevated the pressure in the carotid artery of the rat with a pump and, within 3 or 4 days, noted lesions in the vessels of the kidneys. I hope Dr. Koletsky will comment a little more on this.

LOUIS TOBIAN (Minneapolis, Minn.): I find it difficult to avoid the evidence of the experiments of Robert and Nezamis (*Experientia*, 13:457, 1957) in which they ligated one carotid artery and not the other while inducing DCA-salt hypertension in rats. They observed extensive lesions on the side of the brain in which the full pressure was perfusing the hemisphere. However, on the other side, where the pressure was abated, but where various biochemical constituents were still present, they observed very few lesions. The most obvious difference between the two sides was one of blood pressure.

EDWARD RADFORD: In a fairly large series of rats with latex encapsulation of the kidneys, sacrificed about a year after encapsulation, we found no correlation between the incidence of mesenteric arteritis or generalized vascular disease and blood pressure obtained prior to autopsy. Wissler (personal communication) has observed the same lack of correlation between vascular disease and blood pressure in a larger group of rats. This does not necessarily refute what Dr. Tobian has said because the presence of a moderately elevated blood pressure may be required for the development of a full-blown lesion. There are reports in the literature of regression of eye ground changes in untreated human patients with no change in blood pressure. Perhaps some of you have had direct experience with this question.

LEWIS DAHL: Relative to Dr. Koletsky's point, I have long believed that sodium had a very basic function in the diseases of the blood vessels associated with hypertension. We, too, have frequently observed the phenomenon of fundi clearing up with no apparent diminution of blood pressure, and I think this is a common observation of most people who have clinical experience. Therefore, my own belief is that patients whose blood pressure does not respond to sodium restriction should still have their sodium restricted.

SYDNEY FRIEDMAN: I want to get into the argument about eggs and chickens, but only indirectly. Relative to the possible actions of salt, it is one thing to talk about salt and another thing to talk about the mechanism involved. If one starts with the fact that the contractile machinery is in the smooth muscle cell, one can assume that, in general, it is probably similar to the contractile machinery in other types of muscle and that ionic distribution probably is involved. Generally speaking, one isn't then surprised that the systems which control the distribution of salt and water must necessarily be involved in the regulation of blood vessel tone. We have directed our work at the muscle cell and have attempted a study of the interrelation of the three basic salt and water control mechanisms—the kidney, the adrenal and the neurohypophysis. We are concerned with their interrelationship in determining the final end product across the cell. These three are discussed as if they were all independent,

but if one is dealing with a control system they can't be independent; they must function in an interdependent manner. We have paid particular attention to the neurohypophysis-mineralocorticoid relationship and noted that there seems to be a seesaw relationship. Ordinarily, when you administer a mineralocorticoid such as DCA, you suppress the neurohypophysis. There is a delay period preceding the onset of the blood pressure rise and this delay period is slightly exaggerated if the animal is neurohypophysectomized. If minute amounts of vasopressin are administered with the DCA in this initial stage, one can abolish completely the delay period in the onset of DCA hypertension (Friedman, S. M., et al., *Endocrinology*, 67: 752, 1960), indicating that there is a correlation between the two functions. In so far as transmembrane distribution of ions is involved, it can be shown that the net effect (nothing to do with mechanism) of vasopressin given with DCA or vasopressin with aldosterone is additive as if both were acting in the same general direction (Friedman, S. M., et al., *Am. J. Physiol.*, 199: 1195, 1960). Thus, in acute experiments one can demonstrate a shift of sodium across the cell membrane induced by vasopressin, and if the animals are pretreated with DCA, this is remarkably exaggerated long before the blood pressure has increased. This can be demonstrated within 5 or 6 days of DCA treatment. Therefore, these functions should not be considered an isolation. Recently, Genest and his colleagues (*J. Clin. Invest.*, 40: 338, 1961) reported a striking observation that angiotensin increases the secretion of aldosterone; thus, they have tied the adrenal-kidney control mechanisms together. We haven't a clue about the feedback system. If we just define the control mechanism, however, we know there must be feedback.

Does anybody know what feeding excess salt does to vasopressin levels? Ordinarily, salt feeding is a good stimulus for the secretion of vasopressin. Is this a combination of vasopressin and mineralocorticoid or excess vasopressin alone? I am suggesting that we might stop trying to decide which is the chicken and which is the egg in the question of blood vessel pathology versus rise in blood pressure. For every argument raised in support of one position, an opposite one may be raised for another. In metacorticoid hypertension, which we produced years ago and first called "post-DCA-sustained hypertension" (this is the hypertension which persists after the cessation of acute intense periods of DCA treatment), there is no relationship between vascular lesions and elevation of blood pressure.

MELVIN FREGLY: I do not have the answer to Dr. Friedman's question about the level of vasopressin in animals with salt hypertension but we have tried unsuccessfully to induce salt hypertension in hypophysectomized rats. Admittedly, these animals had more physiologic problems than just decreased blood levels of vasopressin and diabetes insipidus, but we could not induce hypertension even though the experiments were carried out over long periods of time.

CHARLES HALL (Galveston, Texas): We can confirm that. We have not been able to either.

LEWIS DAHL: We have recently labeled antidiuretic hormone (ADH) with tritium and radioactive iodide and studied ADH turnover in dogs fed salt for 5 years as well as in people with and without hypertension. We were not able to discern any effect of salt feeding on turnover of ADH.

FLOYD SKELTON (New Orleans, La.): I have always thought that the dog was more capable of handling a salt load than was the rat, and that in this respect the latter species was much more like man. This may be the reason why the dog is so resistant to the salt-type of hypertension.

Like all morphologists, I have been interested in the question of which comes first, the vascular lesions or the elevation in blood pressure. In association with Drs. Jack C. Geer, Henry C. McGill, Jr. and Issei Nishimori a study was made of the renal changes which occur during the developmental phases of adrenal regeneration hypertensive disease, using both light and electron microscopy, in an attempt to determine whether detectable lesions were present before the onset of hypertension (*Lab. Investigation*, 10: 51, 1961). Although this particular type of hypertension develops rapidly, we believe that the nature of our sampling was such as to give us a reasonable idea of what was taking place. Lesions were found in the glomeruli of control rats which did not become hypertensive as well as in rats bearing regenerating adrenals before there was elevation in blood pressure. The lesion in control rats consisted of lobulation of the glomerular tuft and the presence of homogeneous ovoid bodies in the cytoplasm of epithelial and mesangial cells. Glomerular necrosis occurred infrequently, and then only after 63 days. No arterial or arteriolar lesions were seen.

In rats bearing regenerating adrenal cortical tissue, glomerular changes were the same as in control rats until 14 days after enucliation. Thereafter, the changes became progressively more severe, characterized essentially by necrosis in light microscopy and in the electron microscope, by the accumulation of larger and more numerous ovoid bodies in epithelial and mesangial cells, loss of epithelial cell foot processes and the appearance of dense, finely granular material between normal-appearing basement membrane and mesangial cells. Finally, necrosis of epithelial cells occurred and cellular debris was seen in Bowman's space.

Fat droplets were observed by light microscopy in the media of occasional small arteries and arterioles before the blood pressure reached hypertensive levels but it was not until significant hypertension was present that medial necrosis appeared prominently. The severity of this change progressed about in

proportion to the rise in blood pressure. In the electron microscope the process of necrosis was characterized by increased cytoplasmic density, the presence of dense, irregular particles and ovoid bodies completely or partially surrounded by a limiting membrane occasionally containing fragments of membranous material within their substance. It is our present belief that the glomerular and arteriolar changes are separate phenomena.

A recent paper by Okata et al. (*Proc. Soc. Exper. Biol. & Med.*, 102: 187, 1959) is germane to the question of whether hypersensitivity is involved in the development of the polyarteritis type of arterial lesions. In rats with DCA hypertension these investigators were able to localize gamma globulin in the walls of damaged arteries by the fluorescence antibody technic, yet they suggest that antibody may not be required for this process. The true significance of this observation must await further study.

Another point in question in the genesis of vascular lesions of hypertension is the elevation of pressure *per se*. The first report in which elevation of blood pressure was induced by mechanical means (Byron, F. D. and Dodson, L. F., *J. Path. and Bact.*, 60: 357, 1948) suggested that it could produce the necrotic and proliferative lesion called polyarteritis in the rat. Although these lesions were certainly polyarteritis it has always seemed doubtful to me that they could have arisen in the time between elevation of the intravascular pressure and sacrifice of the animals. Furthermore, the method of raising intravascular pressure was simply to inject physiologic saline into the renal artery from a syringe. This, of course, produced only a transitory elevation in pressure, even though repeatedly done, and the magnitude of the elevation was totally unknown and totally uncontrolled. Similar experiments have been done in at least two other laboratories. Masson, Corcoran and Page (*Rev. Canad. de Biol.*, 10: 309, 1951) observed vascular lesions in a few animals following elevation of intravascular pressure but Schaffenburg and Goldblatt (*Proc. Soc. Exper. Biol. & Med.*, 96: 421, 1957) completely failed to produce arterial necrosis by elevation of the intraarterial pressure alone. Personally, I am more inclined to accept the results of these latter investigators because their methods allowed for better control of the increase in pressure and the increase was greater than that produced by previous workers.

Thus, if pressure change is involved in the production of arterial necrosis it may depend upon the rapidity at which the pressure rises, the duration of the pressure increase, the pulse pressure or other factors.

I would like to ask two questions. Are there differences between the sexes in the development of either salt hypertension or DCA hypertension? Has anyone been able to induce hypertensive disease by pituitary preparations which presumably would act through endogenous secretions of adrenal steroids, and if so, was there any sex difference?

CHARLES HALL: In reference to distribution of lesions as they pertain to DCA and salt hypertension and to a lesser extent to the salt hypertension we have seen in our laboratories, I have not yet seen a case of the periarteriolar type in the mesentery and pancreas or elsewhere in an animal which was not hypertensive. On the other hand, I have seen hypertensive animals that did not show such periarteriolar lesions. The assumption is that one has to have hypertension in order to get these lesions, but that they are not dependent upon hypertension itself, rather on some other factor which may go along with it. In respect to salt hypertension as such, we have not studied this specifically, but recently we had occasion to run a long-term salt control for other experiments. I have seen individual cases of glomerular sclerosis in animals without their ever having been hypertensive; most of them are entirely normal. If one looks at the heart, one finds that it is possible to get necrotizing vascular lesions with the usual granulomatous changes in hypertensive animals which have been hypophysectomized and given DCA and salt. On the other hand, when we have studied the metacorticoid forms, we have seen no cardiac lesions whatsoever. The assumption must be that they have had them and they went away; I can see no other explanation for this. We have been unable to find the scar tissue which was left behind after they regressed. Even though they had a higher blood pressure for a longer time, they did not have cardiac lesions, but the mesenteric lesions were phenomenal and the renal lesions were minimal.

HOWARD SWANN (Galveston, Texas): May I ask Dr. Dahl a question? Abrams and associates (*Am. J. Physiol.*, 156: 233, 1949) reported on the salt appetites of rats with experimental hypertension which were exactly the opposite from hypertensive human subjects. The hypertensive rats do not like salts as much as the normal rats.

LEWIS DAHL: Many people have asked me this question and my only answer is that rats are really smarter than human beings. I don't have any answer except that there are suggestions that this may not be true!

ARTHUR GROLLMAN: Dr. Wilgram, did I understand you to say that you were disturbed at not being able to implicate the kidney? Certainly you revealed enough lesions in the kidney! Moreover, one can induce hypertension in the dog after removing the adrenals and without any added salt. In your experiment, removal of one kidney involves renal damage as well as any observed morphologic damage to the blood vessels!

GEORGE WILGRAM: This morning I was impressed that the emphasis on the primary site of the damaging effect of salt was shifting away from the kidney toward the peripheral vascular bed. While I cannot dispute the importance of the peripheral vascular bed in salt hypertension, the kidney showed such dramatic changes in our experiments that I feel our results

might support some of the older views on the pathogenetic importance of the kidney in salt hypertension. The primary damage in the kidney might occur either in the glomerulus or in the tubules but it is more likely in the former.

ARTHUR GROLLMAN: Dr. Koletsky, there is a serious objection to your interpretation of the experiments in which you removed the kidneys and administered salt; namely, the confusion of an elevation of blood pressure with hypertension. A normal animal, if overloaded with salt, may show a rise in blood pressure, but one should not conclude that hypertension has been induced. The salt cannot escape once the kidneys are removed, hence, the elevation in blood pressure. To designate the observed elevation in blood pressure as hypertensive disease and draw any conclusions regarding this disorder as it occurs in human beings is mere sophistry.

SIMON KOLETSKY: First, I hope I have said nothing that will be construed as opposed to the role of the kidney in hypertension. I have no doubt that an important cause of hypertension is renal injury. The issue involved is whether a disease called essential hypertension in man has a primary renal basis.

Dr. Meneely's point on two kinds of hypertension has not been clear to me. When we salt load rats chronically, we get instances of high blood pressure without significant vascular disease. When there is such disease in benign hypertension, it is the same kind as seen in the so-called malignant phase. I do not believe that there are two kinds of vascular lesions which accompany hypertension in the rat, and I am not sure as to how any method of producing high blood pressure in the rat can be divided into benign and malignant forms in the sense that the morphologic vascular lesion is different as it is in man. The necrotizing element in man in the malignant stage is not seen as a rule in the benign phase.

Those of us who feel that high blood pressure is not necessarily the cause of vascular disease are in the minority. In Cleveland one camp believes hypertension to be the cause of vascular diseases and the other camp is not so sure. The evidence to be derived from excess pressure is not too good. Johnson and Moore (*Proc. Soc. Exper. Biol. & Med.*, 79: 138, 1952) and Muirhead et al. (*Arch. Path.*, 50: 137, 1950) have been unable to confirm it. I have seen slides in some instances in which lesions were claimed to have resulted, and I have not been entirely confident of the investigator's results. I hope I was not prejudiced at the start, because I think one has to look at this material with great care. One valid line of evidence that hypertension causes vascular disease is the clip. When you put a clip on an artery the yield is a hypotensive situation beyond that clip. However, a clip does more than induce hypotension; it changes rates of flow and it may change chemical composition of the blood. This goes back to Wilson and Byrom's experiment with unilateral clips (*Quart. J. Med.*, 10: 65, 1941). A clip on one renal artery yields renal hypertension in the rat. Vascular disease does not develop in the protected kidney whereas the unprotected kidney deteriorates. However, if you take out the unprotected kidney, the protected kidney will then light up with striking vascular disease, but the clip is still there and it should still be protecting the organ.

DAVID GORDON (Miami, Fla.): This is only a relative protection. The pressure must be low but only relative to the pressure on the other side. It must be 180 mm. Hg on one side and 200 on the other.

SIMON KOLETSKY: They went beyond that argument and suggested that the vascular constriction developed in the clipped kidney. The only point I would like to make is that in an experimental set-up like this, you are now adding other etiologic possibilities when the unprotected kidney is removed. You add the possibility of a renal contribution to the lesion and the possibility of the renal disfunction as well as the factor of altered blood flow. At any rate, there is a difference of opinion here, even though the view of the majority is that hypertension is the culprit.

Dr. Skelton has said a number of things with which I can agree *in toto*. There are early changes that antedate the hypertension as shown by special technics, one of which is electron microscopy. Rather than talking about the hypertension causing the vascular disease, perhaps we may have to switch the table around. I think most of us will agree that polyarteritis is not due to hypersensitivity. I agree with Dr. Hall in that I too find it difficult to demonstrate these lesions if the animals are not hypertensive. However, I don't think that this necessarily means that therefore they are caused by the hypertension.

In reply to Dr. Grollman's comment on removal of the kidneys and then adding salt, when I take three-fourths of the total kidney mass out and load the rat with salt, I do believe that I am inducing hypertensive cardiovascular renal disease in the true sense.

ARTHUR GROLLMAN: How long do you wait after you do this? Only for short periods, as I recall your illustrations.

SIMON KOLETSKY: Yes, I get lesions within a week or two. This is a replica of salt hypertension, only accelerated in form.

ARTHUR GROLLMAN: The matter of time is an important point of differentiation. In the human being we are dealing with a chronic disease which goes on for years; to merely induce an elevation of pressure, albeit accompanied by vascular lesions, does not imply that you are inducing the same disease. There has been confusion in relating the "malignant" to the so-called "benign" stage of essential hypertension. There is nothing "benign" or "essential" about a disease which is going to kill

you! There is nothing "malignant" about it except that it is usually fatal!

Incidentally, the results on the dog surviving 10 years of hypertension and not showing any lesions leave some question in my mind. All studies indicate that the lesions appear long before the 10 years are up. Even studies of so-called "neurogenic" hypertension from Schroeder's group indicated also the presence of lesions; but we found none in our animals and do not believe that this preparation represents true hypertensive disease. If you pet the animals or have them run around the building for exercise, you will find their blood pressure comes down to normal. It is only when you excite them after removing the buffer nerves, that you get these elevated pressures. I don't consider that hypertension. We have found cardiac hypertrophy, which is certainly an organic change, in all hypertensive dogs kept for any length of time. One would anticipate that the vascular changes in the rat might be different from those in the human subject and one could hardly expect identical changes in the vessels of a rat and human beings. The existence of certain morphologic differences is no valid ground for denying the fact that we are dealing with the same disease.

The Role of Salt in Health and Disease*

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Dallas, Texas

SODIUM CHLORIDE, commonly designated as "salt," has been a constituent of the environment of living things from the time of their first appearance in the primeval oceans. According to geochemists, the first oceans were perhaps less briny than they are now, but, in any case life began in a salty marine environment and it is not unexpected that this highly diffusible substance should have become a basic constituent of our unicellular ancestors and an essential component of all protoplasmic systems. When the marine environment was ultimately abandoned, salt remained as the principal inorganic constituent of the extracellular fluid in which the cells of the organism were now immersed. Salt water surrounds every cell of our body as it did in our most remote ancestors.

Salt has occupied a place of importance from the earliest times of recorded history as may be noted from allusions to it in early literature and the proverbial and allusive senses in which the term "salt" is used in many languages. The association of salt with the sea is the basis for the origin of the word from the Greek for sea, and from which the term halite is also derived. The piquancy of salt led to its association early with pleasures of the mind, effusions of wit and the amenities of life, as reflected in such expressions as "salt of the earth," "the saltiness of youth," etc. The American Indian called it "white magic."

Primitive man no doubt cherished salt and used it whenever available. Archeologic evidence indicates its use in the cooking of wheat and barley by cavemen 5,000 years ago and records of its production by solar evaporation and mining go back to earliest times. Nevertheless, certain ethnic groups apparently never had contact with it.

DIETARY USE OF SALT

The salt intake varies considerably in various communities. The French are reputed to add 3 per cent of salt in their baking, whereas in the south of England very little salt is used for this purpose. It is generally stated that the average intake of salt by the American populace is about 5 to 10 gm. per day, but my analysis of the urinary salt output of a series of patients indicated a daily intake from a minimum of 3 gm. in those avoiding the addition of salt to their food to as high as 30 gm. in those who admittedly used it profusely. The majority of subjects took from 7 to 15 gm. of salt daily.

It is generally believed that the craving for salt by different peoples depends on the nature of their diet. Cereal and vegetable diets stimulate the desire for salt; pastoral populations living on animal diets require none and hence crave no salt. The Kirghizes of Turkestan and the Bedouins of Arabia, for example, are said not to utilize salt, the latter finding its use ridiculous.

Wild animals, which unlike man often show an instinctive intelligence towards their diet, have a great fondness for salt and travel long distances to salt licks in order to satisfy this taste. However, this is only true of the herbivora whose salt intake is normally low but whose potassium intake is very high. A marked deficiency of salt interferes with the growth and milk output of dairy cows and, when extreme, may lead to serious illness. The carnivora, as might be anticipated, need no added salt and show no craving for it.

The appetite for salt manifested by the human being appears to be an acquired habit rather than a reflection of any innate need for this substance. Young children show a dislike for salted food when first presented with it. Since salt adds to the piquancy of many articles of food, it is not surprising that it has assumed an important place with other condiments in the culinary arts. On the other hand, the indiscriminate use of salt as well as of other con-

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diments destroys the natural flavor of foodstuffs and its avoidance for reasons of health involves no great sacrifice.

General Biological Considerations

Salt is an ubiquitous constituent of all plants and animals as well as of their terrestial environment. As the chief electrolyte of the extracellular fluid its concentration is of vital importance in maintaining the functional integrity of the cells; constancy of the sodium and chloride content of the body constitutes one of the important factors in homeostasis. In so complex a mechanism as the living body this constancy of the internal environment must be maintained within very narrow limits and deviations of only slight degree will result in marked dysfunction, and when extreme, in the death of the organism.

Distribution in the Body

The total sodium and chloride contents of the body increase in parallel fashion as the fetus grows, reaching maximum concentrations of 94 to 118 mEq. per kg. for sodium and 69 to 76 mEq. per kg. for chloride at about the fifth month of intrauterine life. Thereafter, the concentrations decline until at term the infant contains about 76 mEq. per kg. of Na and about 50 mEq. per kg. of Cl. This decline continues with growth and age and is more pronounced for chloride. Dilution technics with radioactive Na and Cl have been used to determine the total exchangeable amounts of these ions which are metabolically and functionally active in the body. Such studies indicate that considerable amounts of sodium are fixed in tissues, chiefly bone. For chloride, the dilution values which are close to absolute values for the total amount in the body in the newborn also show a slight divergence in the adult, indicating the presence of some chloride in a fixed nonlabile form.

Sodium and chloride are the most abundant inorganic elements present in the extracellular fluid, being present in blood plasma in a concentration of about 140 and 100 mEq. per L., respectively; their concentration in the intracellular fluids is only about a fifth as large. The maintenance of this physicochemical disequilibrium between the cells and their environment necessitates the expenditure of energy and attention has been given recently to the elucidation of the mechanism of the "sodium pump" whereby sodium is excluded from the cell. A notable exception to the low intracellular content of sodium is shown by the red blood cells of the dog, cat, goat and sheep, in which species sodium is the main intracellular cation rather than potassium as in man and other species. The significance of this difference is unknown.

Physiologic Role

Since sodium chloride is dissociated in aqueous solution to form sodium and chloride ions, it does not exist as an entity in the body and we must consider its constituent ions separately insofar as their effects on the organism are concerned. Since sodium and chloride constitute most of the ionic constituents of extracellular fluid, they will play the major role in determining the osmotic pressure of this body fluid compartment and in considering osmotic relationships one may disregard such other ions as potassium, calcium, magnesium, bicarbonate, etc., which are present in relatively small amounts. Sodium and chloride will thus be concerned intimately with the control of the volume of the interstitial fluid and of the water content of the tissues, with the maintenance of the volume and pressure of the circulating blood and with the regulation of the total amount and distribution of the body water.

Relation of Na to Other Ions. In addition to its described role as an osmotic regulator, the sodium ion also is concerned in several more specific actions involving various vital processes. It has thus long been known that the irritability of protoplasm and the capacity of unicellular organisms to live in fluids of varying sodium content depend upon the concentration of this ion. In this respect, however, sodium does not play an independent role but is intimately related to the other ionic constituents which must be in a fixed relationship in order to maintain normal physiologic activity. Na ion leads a separate existence in solution but is affected by the presence of other ions. Consequently, we must always consider the relative concentration of Na^+ to K^+, Mg^{++}, Ca^{++} and H^+ in evaluating their functional effects. Thus, the irritability of cells, as reflected, for example, in the electrocardiogram, will be determined not only by the level of the K^+ present in the plasma but also directly with the Na^+ and inversely with the Ca^{++} and Mg^{++} concentrations. Thus, the classical effects of hypokalemia on the electrocardiogram may be absent

in the face of hypernatremia, hypocalcemia or hypomagnesemia.

The interrelationship of sodium to other ions is also evident in its behavior particularly in the kidney in which the production of an acid urine and the excretion of potassium are dependent upon an exchange of sodium for hydrogen and potassium ions, respectively. One finds, accordingly, that the effects induced in certain abnormal states will be dependent upon the availability of sodium. In the case of potassium depletion, for example, one observes very little symptomatic effect, despite a marked potassium deficit in the cells, if the sodium intake has been maintained at a low level. On the other hand, in the presence of a high sodium intake, sodium enters the cell and the characteristic symptoms of potassium-depletion appear. Likewise, patients manifesting tubular acidosis may be maintained in a relatively good condition if their sodium intake is restricted. On the other hand, if sodium is given, there is a loss of sodium bicarbonate in the urine and acidosis with its accompanying symptoms appears.

Role of Na in Extracellular Fluid Osmotic Pressure and Volume: Sodium accordingly may be considered as exerting a dual role in the organism. As a constituent of protoplasm and as the major cation of plasma it must be looked upon as an important structural part of the living organism. In the extracellular fluid it constitutes the main cation which determines the osmotic pressure of this body fluid. Deviations in its concentration by altering the osmotic pressure will result in the transfer of water between the cellular and extracellular space and give rise to the phenomena of dehydration and edema observed in disease.

Since each gram of salt is accompanied by approximately 125 ml. of water, the loss or accretion of only 8 gm. of salt will result in the loss or gain of a liter of water—a considerable quantity when one considers the total water content of the body. The loss or gain of this amount of fluid from the extracellular space is mitigated however by the exchange of water between the relatively small extracellular and the much larger intracellular compartment which accordingly can act as a buffer and reduce the otherwise catastrophic effects of large changes in volume of the vascular space. This buffering capacity, however, is limited to water, losses or gains of which impose only minor changes in the volume of the extracellular fluid. Since sodium, unlike water, is excluded from the intracellular compartment, alterations in the body content of this cation result in marked changes in the volume of the extracellular and vascular spaces and bring about drastic effects on the circulation.

Na in Acid-Base Balance: Salt, as already indicated, plays an important role in the maintenance of the normal acid-base balance by the stabilizing action of the sodium buffer systems present in the extracellular fluids. Sodium bicarbonate serves to carry the principal acid of body metabolism, carbon dioxide, to the lungs. The interaction of sodium ions with disodium phosphate and with the serum proteins helps to maintain neutrality in the body. In addition, sodium exchanges for hydrogen and for potassium in the distal tubule and it is evident therefore that the quantity of sodium in the tubular fluid will determine the rate of excretion of both potassium ions and hydrogen ions. This accounts for the potassium losing effect of large doses of sodium salts and the exacerbation of potassium deficiency by a high salt diet as well as for the effect of a high salt intake on the excretion of sodium bicarbonate in tubular acidosis.

Normal Control of Sodium Metabolism

Kidney: The sodium content of the tissues and body fluids is maintained normally at a very constant level by balance of the amount ingested and that lost from the body. The principal avenue of excretion is by the kidney, only small amounts being excreted normally through the bowel (50 to 100 mg. per day) and perspiration (15 to 80 mEq. per L.) except at high environmental temperatures or during heavy work. The kidney acts as the chief control of the sodium content of the body and it is through the action of this organ that the accumulation of sodium in such conditions as congestive heart failure is mediated. When the sodium intake is reduced or when the kidney is activated to retain sodium, this organ has the capacity to reduce the sodium output to almost negligible quantities, a capacity not manifested towards potassium. It is for this reason that in the presence of normal renal function and in the absence of abnormal losses through the bowel or skin, drastic sodium restriction results in no serious sodium deficiency.

Adrenal Cortex: The kidney in turn is regulated in its control of sodium excretion by the adrenal cortex, by changes in vascular hemodynamics,

and by action of the central nervous system as well as possibly by other unknown mechanisms. Exactly how these act is not known although much work has been carried out to elucidate the problem. The adrenal cortex mediates its effects on the metabolism of sodium not only through its action on the kidney but also by a direct effect on the sodium content of other tissues as has been demonstrated by studies on the nephrectomized animal. Desoxycorticosterone and aldosterone, the mineralocorticoids, induce sodium retention and potassium excretion by their action on the tubules. The retention of sodium observed in congestive heart failure, cirrhosis of the liver and nephrosis is in part at least mediated by the increased secretion of aldosterone which occurs in these disorders. The adrenocortical mechanism thus operates to conserve body sodium and thereby blood volume and ionic balance between the cells and their environmental fluids.

In the absence of any abnormal losses of salt from the body as in excessive sweating by unacclimated subjects there is no need for supplementing the intake of salt since normally the amount present in foods far exceeds the needs of the body. The capacity of the kidney to excrete salt is also of such magnitude (300 mEq. per L.) that it is difficult to ingest an intolerable amount, particularly since thirst is stimulated in the process. However, it does not follow that such excessive chronic intake might not eventually induce injury and participate in the pathogenesis of hypertension and atherosclerosis as has been demonstrated to occur in the rat.

Abnormalities of Sodium Metabolism in Disease

A number of diverse experimental and clinical conditions induce a deviation in sodium metabolism. Excessive sweating may under extreme conditions cause the loss of as much as 30 gm. of salt per day; diarrhea and vomiting may under extreme conditions result in the loss of as much as 50 and 25 gm., respectively. The chief sources of loss observed clinically are through the kidney as in adrenal cortical insufficiency, acidosis, salt-losing nephritis, the administration of excessive amounts of diuretics and cerebral disease. Loss of sodium may also occur through abnormal channels as in hemorrhage, from wounds, ulcers, fistulae or surface burns. Losses may be induced by suction drainage of the stomach or intestine or by paracenteses. All such losses will of course be aggravated by a low sodium intake, a not uncommon occurrence in patients not eating and depending upon parenteral fluids and alimentation.

One may observe in serious illnesses a decrease in the plasma sodium with loss of potassium from the cell and an increase in its sodium content. Tissue injury, as in massive burns, prolonged anoxia, exposure to cold, etc., may result in a similar condition which reflects presumably a loss of the normal capacity of the tissues to maintain a high sodium gradient across the cellular membrane. A decline in plasma sodium is frequently observed in moribund patients, reflecting the loss of this capacity by the dying cell.

Sodium retention occurs in a variety of clinical conditions, notably in congestive heart failure, diseases of the kidney, nutritional edema, cirrhosis of the liver with ascites, and toxemia of pregnancy. Normal pregnancy is associated with some salt and water retention with diuresis following delivery. There is no reason to believe that the retention of salt in any of these conditions, except renal diseases, is a consequence of the inability of the kidney to excrete salt. On the other hand, there is good evidence to support the view that the retention of salt by the kidney in these conditions is secondary and teleologically may be looked upon as a compensatory mechanism to increase the circulating fluid volume.

Therapeutic Considerations

The physiologic role of sodium in the normal state and the deviations observed in disease would lead one to anticipate that changes in the intake of sodium might be of therapeutic importance. That this is the case can no longer be questioned although it is only recently that scepticism concerning the value of sodium restriction has been dispelled and that this has become a therapeutic measure of importance.

The therapeutic value of administering salt in conditions of sodium depletion has been readily accepted because of the immediacy with which the benefits of such therapy are attained. Notable examples of such losses through the kidney, gastrointestinal tract or skin, respectively, are afforded by Addison's disease, cholera and excessive sweating which, as already indicated, results in reduction of the extracellular and vascular fluid volumes with deleterious effects on the cardiovascular

system. The administration of salt to correct the deficiency results in dramatic improvement. Other conditions associated with loss of electrolytes and water, such as in diabetic acidosis, respond equally well.

The restriction of sodium in the diet is less easily accomplished without recourse to monotonous diets because salt is added to most processed foods. Ignorance as to the sodium content of food results in the ingestion of quantities of salt far in excess of the amount which will result in a negative salt balance. Unless diets are scrupulously ordered and the urinary output of sodium determined as a check on the assumed intake, there is no assurance that the patient is actually on a salt-restricted diet. A failure to appreciate this is responsible for the denial of the benefit of sodium restriction, particularly in such conditions as hypertension, and the indifferent success of such therapy in congestive heart failure, ascites, etc.

Because of the difficulty of restricting sodium in the diet, as just outlined, the first demonstrable benefits of sodium restriction clinically were obtained by the use of such simplified diets as the Karrel milk diet, Kempner's rice diet or fruit diets, but those originally advocating the use of such diets failed to appreciate the fact that their efficacy was due to the low sodium content.

The rice diet consists of 300 gm. rice daily with fruit and fruit juices supplemented with sugar, iron and vitamins. The caloric intake per day is adjusted to individual requirements, providing about 29 gm. protein, less than 3 gm. fat, 420 to 570 gm. carbohydrate and 2.5 to 7 mEq. sodium. The diet allows adequate calories but is virtually free of sodium, fat and cholesterol and provides a minimum of protein. Such a diet is unpalatable, monotonous and almost impossible to maintain except under special circumstances. When a normal subject or a hypertensive patient not in congestive failure and with well-preserved renal function is placed on the rice diet, the urinary excretion of sodium falls virtually to zero within 24 to 48 hours because of the extraordinary capacity of the kidneys to conserve sodium. As a result, even after months on the diet, the serum sodium drops little if at all. However, if the kidneys are damaged, as in glomerulonephritis or advanced nephrosclerosis, sodium is often lost in the urine and circulatory collapse may follow. This may occur also in congestive failure if diuretics are used too assiduously in conjunction with rigid sodium restriction. Neither the rice-fruit diet nor the low sodium diets change the serum potassium levels in congestive heart failure. However, in the presence of renal insufficiency, the high potassium content of fruits and fruit juices may induce dangerous hyperkalemia. A moderate degree of hypochloremic alkalosis often develops on the rice-fruit regimen, probably because of the high intake of organic acids in fruit and fruit juice. This does not occur on ordinary low salt diets.

The therapeutic effects of the Kempner diet or of sodium restriction in essential hypertension and congestive failure intractable to other forms of treatment are striking. Persistent orthopnea, dyspnea and edema disappear and cardiac dilatation is diminished. The diets also have impressive effects on symptomatology, hypertension, electrocardiographic changes, cardiac enlargement and retinopathy of some patients with severe and protracted essential hypertension in whom congestive failure is not a prominent feature. In order to achieve these responses in essential hypertension it is necessary to restrict the sodium drastically. Less drastic restriction is required in congestive failure, many patients responding to diets containing 1 gm. of sodium chloride or even more.

CONGESTIVE HEART FAILURE

The importance of sodium restriction in the management of congestive heart failure is so well established and generally accepted that it need be considered only briefly here. There has been a renewed interest recently in the importance of a large intake of water as part of this regimen not only in congestive heart failure but also in the other conditions treated by sodium restriction. Such combined therapy together with a high potassium intake has been advocated for angina pectoris as well as for hypertension.

Although several factors are concerned in the retention of salt and water in congestive heart failure, the retention of sodium by the kidneys is one of the earliest manifestations of circulatory incompetence as demonstrated by Barger and his co-workers. In fact, retention of sodium precedes any measurable rise in venous pressure and is present even before there is a demonstrable decrease in glomerular filtration rate. However, there is a demonstrable decrease in renal plasma flow and it is possible that a significant decrease of the glo-

merular filtration rate not detectable by present methods is responsible for the retention of sodium. In any case, it is apparent that in circulatory failure the kidney responds by retaining salt and water which accumulate in the body as edema.

HYPERTENSION

Sodium Restriction and Sodium Depletion: The role of sodium in the pathogenesis of hypertension and of sodium restriction in the treatment of this disorder has stimulated many studies. Since many of these will be considered by other speakers in this seminar, only the salient points need be considered here. Sodium occupies so vital a role in the animal economy that it is not surprising that its restriction should affect so labile a function as the blood pressure. Grollman and Harrison, in 1945, demonstrated the effectiveness of sodium restriction in lowering the blood pressure and prolonging the survival of hypertensive rats. These authors applied this procedure to hypertensive patients and demonstrated that it was necessary to restrict the sodium intake drastically in order to elicit a drop in blood pressure and that moderate restriction was of no avail for this purpose. They demonstrated for the first time that it was the sodium rather than the chloride ion which was responsible for the hypotensive effects of salt restriction and that the intake of sodium salts such as sodium bicarbonate or sodium phosphate, previously allowed to patients on a low salt diet, would counteract any effect of salt restriction. They demonstrated also that the virtue of the rice diet of Kempner was attributable to its low sodium content rather than to any specific virtue of the rice, as had been previously claimed; that lowering of the blood pressure could be induced by the use of any monotonous diet such as the ingestion of potatoes, peanuts, soybeans, etc.; and that the addition of salt to rice would result in the prevention of its hypotensive effects. With the introduction of the potent orally effective benzothiadiazine and phthalimidine diuretics, it became possible to induce sodium depletion with relative ease so that at present there is no longer any doubt as to its effectiveness. This consequently has been adopted widely as one of the most effective and safe procedures for treating hypertensive cardiovascular disease.

Sodium-Induced Hypertension: Not only is the restriction of sodium effective in lowering the blood pressure in hypertension, but the administration of excessive amounts of sodium in the diet induces a chronic elevation in blood pressure in the experimental animal. This has suggested that the ingestion of excessive salt may also play a role in inducing hypertension in the human. Steroids, notably desoxycorticosterone, which induce sodium retention were noted early to cause an elevation in blood pressure when administered in excessive doses with salt to the human subject. In the rat a similar elevation in blood pressure was demonstrated to occur following the administration of various steroids even when the intake of sodium was not excessive. The combination of steroid, excessive sodium and unilateral nephrectomy greatly intensifies the vascular damage and the elevation in blood pressure. The hypertensive effect of salt and unilateral nephrectomy may also be intensified by enucleation of the adrenal, which presumably acts by further intensifying the disturbance in electrolyte metabolism.

Role of Other Electrolytes in Hypertension: Although most attention has been devoted to the sodium ion in its relation to blood pressure, one would anticipate that alterations in the intake of other electrolytes normally present in the cell would likewise affect the blood pressure. Of the cations, sodium and potassium are frequently inversely affected in the organism, a loss of one ion being counteracted by a gain in the other. The deleterious effect of the sodium ion in elevating the blood pressure and inducing vascular damage may be counteracted by the simultaneous administration of large amounts of potassium. Relatively little attention has been paid to the effect of anions on the blood pressure, although these would be expected to influence to some degree at least the action of the cations with which they are associated. Selye and his collaborators have demonstrated that not only does the relative amount of potassium present in the diet determine whether the sodium ion will induce its sensitizing action but that the nature of the anion combined with the sodium plays an important part in determining the severity of the reaction. Thus, sodium phosphate or sulfate is more effective in inducing lesions in the heart and blood vessels than is sodium chloride.

Mechanism of Action of Sodium: As regards the mechanism whereby sodium and other electrolytes modify the blood pressure, it

is necessary to differentiate between the direct deleterious and permanent effects of drastic restriction or excessive feeding of an ion and the temporary effects on the blood pressure of a less drastic and prolonged alteration in the intake of the ion. Thus, excessive amounts of salt administered for many months to the intact rat or for shorter periods in the animal sensitized by unilateral nephrectomy and the administration of mineralocorticoids induces obvious lesions in the cardiovascular-renal system, presumably by direct injury to the cell. There is evidence to indicate that sodium deprivation reduces the blood pressure by diminishing the plasma volume which has been shown to be expanded in the hypertensive. Similar changes follow the administration of benzothiadiazine derivatives, which presumably exert their hypotensive action by their natriuretic effect. Protracted administration of these drugs or continued sodium restriction induce other changes (probably in the composition of the tissues) which maintain this lowered blood pressure.

ROLE OF SALT IN RENAL EDEMA

The retention of salt and water with the production of edema may be encountered in any form of renal disease, but is most commonly seen in *acute glomerulonephritis* and in the nephrotic states. In the former the edema is usually of short duration and is accompanied by hematuria, proteinuria and hypertension. There has been considerable argument concerning the pathogenesis of this edema; it probably reflects a combination of several factors, viz., myocardial failure, expansion of the vascular space, abnormal permeability of the capillaries, the specific glomerular lesion in the kidney which results in a decreased glomerular filtration rate and an increased reabsorption of sodium and water.

In arteriolar nephrosclerosis there is involvement of the kidney with a disturbance in renal function similar to that of chronic glomerular nephritis. Edema occurs in about two-thirds of patients with nephrosclerosis as a consequence of cardiac insufficiency or of an incapacity of the kidney to excrete salt and water normally.

The nephrotic states include a heterogeneous group of disorders, viz., the subacute and chronic stages of glomerulonephritis, lipoid nephrosis, renal amyloidosis, intercapillary glomerulosclerosis, disorders of collagen involving the kidney, certain infections (treponema, plasmodia, leptospira), hypersensitivity reactions to venoms or drugs, poisoning, bilateral thrombosis of the renal veins, etc. This form of renal edema is characterized by massive proteinuria and hypoproteinemia which, in turn, contribute to the severity of the edema. However, the oncotic pressure of the plasma may be reduced to exceedingly low levels without the development of edema if sodium is eliminated from the diet. Conversely, the edema may be reduced without any change in the level of the serum proteins when sodium is excluded from the diet. The view that the kidney in nephrosis suffers from a specific defect which prevents it from excreting sodium has not been established.

Acute renal failure, regardless of its pathogenesis, will be accompanied by edema if this was present prior to the onset of the acute failure, or if it is induced by the injudicious administration of salt or water in amounts exceeding losses by available mechanisms. The restriction of all electrolytes as well as the limitation of water intake to the volume lost by insensible perspiration or other routes from the body is obviously necessary if one is to avoid further accumulation of edema. When the edema is excessive, it may be removed by the use of an extrarenal procedure, such as the artificial kidney, or by intermittent peritoneal lavage.

In chronic glomeronephritis an increased concentration of plasma electrolytes is uncommon; when it occurs it results usually from the ill-advised administration of sodium chloride or of sodium bicarbonate to correct acidosis, or as a result of dietary indiscretion. The excessive administration of isotonic salt solution in the face of impairment of renal function with reduced glomerular filtration rate, combined with water loss by sweating and the excretion of a hypotonic urine, results in hypertonicity of the body fluids and dehydration. Patients with Bright's disease manifesting azotemia usually have a low salt intake because of their poor appetite and consequently may develop hypotonicity of their body fluids. This results in the transfer of water into the cells and the movement of electrolytes from the cells into the extracellular fluid. The intake of water under these circumstances results in retention of water and the development of edema. Although not a common accompaniment of chronic glomerular nephritis, edema does appear at some time in the majority of patients with this disorder. It may be facial or dependent

and usually occurs in association with an acute exacerbation of the disease.

Increased Salt Loss in Renal Insufficiency: Most instances of renal edema encountered clinically are associated with an accumulation of salt as well as of water in the body. However, in certain patients with chronic renal insufficiency, there may be an abnormal loss of salt due to the incapacity of the diseased kidney to retain sodium. This may result in overhydration of the tissues, leading to the edema of water excess. This type of edema of renal origin may be recognized by the clinical manifestations of water intoxication and obviously will be worsened by further restriction of salt. The administration of salt rather than its removal is obviously indicated in the symptomatic management of this condition.

Salt Restriction in Treatment of Renal Edema: As in other forms of edema accompanied by salt and water retention, the limitation of salt intake by dietary measures has long been recognized as a procedure of value in the management of edema of renal origin. Such restrictions may suffice to relieve the edematous state, but, if inadequate, should be supplemented by the use of diuretics. In patients with the more severe grades of renal insufficiency, the restriction of sodium may lead to increasing renal failure and the general manifestations of the sodium deprivation syndrome. Such depletion of salt and water in severe renal disease may in fact precipitate oliguria, as a result of a deficient extracellular fluid volume, and what may appear to be the terminal phase of renal failure.

Whatever the cause of edema, restriction of salt is an important adjunct to treatment because edema fluid is essentially an ultrafiltrate of plasma, and the kidneys will not usually retain water unless salt is retained in the same proportion as it is present in the extracellular fluid. The volume of water retained will accordingly be limited by the dietary salt intake. Where water is retained in excess of salt, hyponatremia ensues. In general, there is a tendency for the development of a mild degree of hypotonicity when the salt intake is drastically reduced. In acute glomerular nephritis the restriction of salt would appear to be desirable even in the absence of oliguria, edema, an elevation of blood pressure or nitrogen retention, in order to counteract the tendency towards hypervolemia and the development of the complications mentioned. In other renal disorders in which there is an elevation in blood pressure, restriction of sodium would also be indicated as in other hypertensive patients. In such patients, however, precautions should be taken against the development of sodium depletion.

OTHER DISTURBANCES IN SALT METABOLISM

Abnormalities in salt metabolism are also encountered in other disorders. *In cirrhosis of the liver* with ascites there is retention of salt and drastic sodium restriction alone will cause the resorption of the ascitic fluid with less possibility of inducing hypokalemia, loss of protein, or other undesirable side effects such as may follow the use of diuretics or paracentesis.

In *fibrocystic disease* and in *adrenal insufficiency*, the loss of salt may induce collapse and remediable effects are obtained by administration of salt. So striking is the response in the case of adrenal insufficiency that following its original observation it was for a time believed to constitute an adequate replacement therapy.

Sodium elimination by dietary restriction and by use of natriuretic agents has also become an important means of controlling such disorders as *premenstrual edema* and *preeclampsia*. However, it must be emphasized that in the latter disorder, despite the amelioration of the symptoms, the basic lesion in the glomeruli is apparently not affected.

Summary and Conclusion

Sodium chloride constitutes an integral part of the living organism and alterations in the concentration of its constituent ions in the body fluids have a profound influence on the animal economy. Such alterations are encountered in many disease processes and their understanding contributes not only to the elucidation of normal mechanisms but also of the pathogenesis of certain clinical disorders and their practical management. Alterations in sodium intake, particularly its drastic restriction, constitute an important part of therapy in several common disorders. Dietary restriction of sodium has certain advantages over the accomplishment of the same result by the administration of natriuretic agents and should be used together with these when indicated.

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Panel Discussion

Chairman: Dr. Melvin J. Fregly

DISCUSSION OF PAPER BY DR. GROLLMAN

ARTHUR CORCORAN (Cleveland, Ohio): How are the kidney biopsies in the preeclamptic patients performed?

ARTHUR GROLLMAN: These were done when the preeclamptic subjects manifested hypertension, edema, etc. (Mautner et al., Year Book of Gynecology and Obstetrics, 1960). All patients were treated with a diuretic with marked clinical improvement. The biopsy was then repeated after delivery; before chronic hypertension developed in any patient. The lesion was still in the glomerular endothelium.

MELVIN FREGLY (Gainesville, Fla.): Is it too early to ask the outcome of your studies in which you fed diuretic agents to pregnant rats?

ARTHUR GROLLMAN: No, it is not. But first, let us clear up the matter of semantics. There are many ways by which one can produce hypertension—metacorticoid, DCA, etc. Many people would like to consider each one as different, but with certain limitations all of these can be explained as results of an action on the kidney. If this be true, anything which modifies this fundamental function of the kidney may result in hypertension. One may injure the kidney by giving an animal a lot of salt, by increasing the intrarenal pressure, by constricting the blood vessels, etc. All these procedures induce injury to the kidney. If one is born with a congenital defect which cannot be seen by the ordinary hematoxylin and eosin stain, this might result in hypertension, and we call it "essential" hypertension. There is nothing "essential" about it; it is congenital. This defect is present at birth and is inherited. It would certainly be of renal origin if it results from glomerulonephritis. We know that there are many other ways of injuring the kidney that may result in hypertension. One can put a clamp on the renal artery and take out the other kidney; it is the taking out of the other kidney which causes the hypertension and not the clamp alone. One can extirpate both kidneys, and the blood pressure goes up. I object strongly to referring to this renoprival hypertension as if it had no relationship to the kidneys. We can produce hypertension by putting an animal on a potassium-free diet when it is young because that also injures the kidneys. When it grows up, hypertension develops just as in the woman with preeclampsia in whom, 10 years later, hypertension may develop and the patient perhaps dies because of the injury which had been done to her kidney originally by the eclamptic process. Choline deficiency injures the liver and kidney and may kill the animal in a week, but if it survives, the liver and the hemorrhagic kidneys recover, and in a few weeks the animal appears perfectly normal. *But*, 6 months later it has hypertension! We know from experience that the younger the animal at the time it is placed on the choline-free diet, the easier it is to induce this effect. That is why we start with weanling rats. We impose a much greater burden on a weanling rat than on an older rat.

We may anticipate that the fetal kidney would be even more sensitive, and on that basis we have attempted and have shown that one can treat a pregnant rat by a variety of measures (all of which presumably affect the fetal kidney) and induce hypertension in the offspring. When we look at the newborn's kidney at birth, it is perfectly normal. At three months its pressure is normal but at 6 months it has hypertension. Here we have a complete analogy to essential hypertension in the human being. The kidney has been injured during embryonic life. One can also give a pregnant animal large doses of one of the natriuretic agents such as chlorothiazide which causes sodium and potassium depletion. One can also inject the mothers with aldosterone or put them on a potassium-free diet, and among the litters which survive there will be a certain number of offspring in which hypertension will develop, due to the fact that we are affecting the kidney at a period in life when it is highly susceptible to injury. If we wait until the same rat is 20 days old, we may have to use the same procedure for perhaps a month before producing an equal amount of injury. The practical implication would be that we shouldn't be too free and promiscuous with the use of drugs in the pregnant woman. That is why I would deprecate the suggestion that all pregnant women be put on chlorothiazide routinely as a prophylactic.

DAVID GORDON (Miami, Fla.): Dr. Wilson in England (*Lancet*, 1: 9, 1958) has shown that applying x-rays to the kidneys will result in hypertension developing 3 or 4 months later.

ARTHUR GROLLMAN: We have tried it in dogs, but unfortunately few survived. It is well known clinically that patients who are irradiated for tumors of the abdomen may have a very severe "malignant" form of hypertension and die (so-called "radiation

nephritis"). Usually the previously normotensive subject suddenly becomes hypertensive and cannot be differentiated clinically from a patient with malignant hypertension except for the fact that you know they were normotensive a month before. There have been a few experiments showing that one can do this in dogs. There is no question about radiation inducing hypertension.

DAVID GORDON: In the adult rat it works fine.

ARTHUR GROLLMAN: Hartman did some work on the effect of irradiation on the rat's blood pressure.

DAVID GORDON: It takes quite a bit though, doesn't it?

ARTHUR CORCORAN: Isn't it in the order of 1800 or 2400 "r," a very large dose to the kidney. If it were given as a total body radiation, it would be fatal.

COMMENT: In renal tissue of dogs, you have to go over 200 "r."

FLOYD SKELTON (New Orleans, La): In the rat, too?

ARTHUR CORCORAN: Yes, it is a high dosage in relation to other tissues.

SIMON KOLETSKY (Cleveland, Ohio): Rats which survive midlethal doses of radiation in about the 500 to 800 "r" range may have what is called nephrosclerosis as one of the late consequences of radiation poisoning accompanied by hypertension. This is probably a renal form of hypertension. It has been described by Nowell et al. (*Rad. Res.*, 11: 545, 1959) and Lamson et al. (*Arch. Path.*, 64: 505, 1957).

EDWARD RADFORD (Boston, Mass.): Casarett at the University of Rochester also described this late renal effect in dogs (*Atomic Energy Committee Report* UR-492, University of Rochester, 1957).

ARTHUR OTIS (Gainesville, Fla.): Would you comment on pulmonary hypertension?

ARTHUR GROLLMAN: The use of the term "hypertension" as synonymous with an elevation in blood pressure has caused no end of confusion clinically as well as experimentally. An elevation in blood pressure represents one hemodynamic factor. If you get excited, your blood pressure goes up, but you don't have hypertension. One can remove the buffer nerves of a dog, its pressure is up because of lack of control, but it doesn't show any of the other changes which occur in hypertension. In coarctation of the aorta there is a high blood pressure in the upper extremities, but that is not hypertension because there is no general increase in peripheral resistance. In "hypertensive disease" we are dealing with a specific disease entity. We have a condition characterized hemodynamically by an increase in diastolic pressure, an increase in peripheral resistance and a relatively normal cardiac output. It is also characterized by a certain clinical course and by a definite pathologic pattern. The pathologist does not have to take the blood pressure of the patient during life; he can look at a slide from any number of tissues and conclude that the patient died from hypertension. Hypertension as a disease has pathologic, physiologic and clinical features that make it a clinical entity. When we induce in an animal a condition which has the same hemodynamic, clinical (insofar as we can compare it) and pathologic characteristics, I cannot see how we can deny that we are dealing with a distinct clinical entity. But we are not relying simply on an elevation of blood pressure. If you take the kidneys out of a rat and pump him full of saline and find his blood pressure is elevated, it is absurd to say you have produced hypertension. You haven't.

Now, pulmonary hypertension represents an elevation in pressure in a particular part of the hemodynamic system, as in the case of coarctation of the aorta, but it does not have these other characteristics and, therefore, is not a form of hypertensive disease. So I would exclude that as I would exclude many other clinical conditions and many experimental hypertensive conditions accompanied only by an elevation in blood pressure. Conversely, the pressure may drop as the hypertensive disease persists. Every hypertensive subject becomes normotensive at least momentarily before he dies, but he hasn't recovered from his disease. Many patients after a stroke or a myocardial infarction will have a normal pressure, but to say that they have recovered from their disease is absurd. They still have their disease but cannot maintain one symptom of it, viz., the elevated blood pressure. We must apply these criteria to our experiments if we are to consider them analogous to the 6 or 7 per cent of humans who suffer from hypertension.

EDWARD FREIS (Washington, D. C.): Is the majority of this 7 per cent suffering from an intrinsic renal lesion at the outset of their hypertension?

ARTHUR GROLLMAN: We can assume that practically all of them are. We have no absolute evidence but as a working hypothesis, we can assume that there is an interference with some renal function not concerned with urinary excretion. There are a few instances, such as the so-called "unilateral" type of hypertension in which there is an infarction of the kidney, possibly also during the phase designated as malignant hypertension, or the hypertension induced by tying a ureter, which have a different mechanism. In these, there is probably an elaboration of a pressor agent, since removal of the tissue cures the hypertension. I think these are different pathogenetically, but they are relatively small in number. The few rare cases of aldosteronism or chromaphil-cell tumors, where removal of the lesion results in a drop in blood pressure, also obviously result from a different mechanism. The great majority of patients with "essential" hypertension are suffering from, I believe, a congenital defect which is renal in origin.

Progress Notes in Cardiology

Edited by EMANUEL GOLDBERGER, M.D., F.A.C.C.

New York, New York

Long Period Continuous Electrocardiography of Active Persons

A NEW AND novel system for continuous electrocardiography of active persons for long periods (10 or 20 hours) was described at the Fourth International Conference on Medical Electronics held in New York recently, in a paper entitled "The Electrocardiocorder and Related Instruments—Applications in Clinical Cardiology" by N. J. Holter and W. R. Glasscock of the Holter Research Foundation, Helena, Montana. The system consists of a self-contained portable recorder which provides many hours of continuous record which is then analyzed, using electronic units which make it possible to screen thousands of electrocardiograms in a few minutes.

Twelve years ago the Holter group proposed and demonstrated the practical use of radio to obtain electrocardiograms from ambulatory subjects to free them from entangling wires (HOLTER and GENGERELLI. *Rocky Mountain M. J.*, September 1949). However, this technic requires radio receiving equipment and a corresponding limitation as to the subject's location. Their next step toward greater freedom was made by using a small radio receiver-recorder carried in a brief case and left by and near a person wherever he was in his normal daily activity. The latest system eliminates the radio transmitter and receiver by miniaturizing the amplifier and recorder into a single small portable unit called the electrocardiocorder (ECC) with an 80 to 100 hour battery supply and a 10 hour tape capacity. The other units, needed to process the voluminous resulting data, are called the AVSEP (Audiovisual Superimposed ECG Presentation Analyzer), (HOLTER, N. J. *Ann. New York Acad. Sci.*, 65: 913, 1957) and the Arrhythmiagraph (ARG) (HOLTER, N. J. and GLASSCOCK, W. R. *Proc. Montana Acad. Sci.*, 18:35, 1958). Chest leads, approximating V_4, are generally used.

The purpose of the electrocardiocorder-analyzer system is not only to eliminate restricting wires or locations but also to provide an opportunity for significantly long periods of continuous electrocardiography as a means of learning more about normal heart action during realistic conditions, and as an aid to the clinician in diagnosing and treating patients with questionable transient cardiac episodes.

The AVSEP unit represents each electrocardiogram rapidly superimposed on its predecessor in such a way that transient abnormalities are readily detected for study. An acoustic signal change is also heard if the electrocardiograms change. A clock unit indicates when the episode occurred. Figure 1 shows a series from a movie of the AVSEP screen showing an anginal attack in a man lifting heavy boxes in the course of his employment (case of Dr. John S. Gilson). The changes are seen in a dynamic manner on AVSEP as the attack occurs. In this case a questionable diagnosis was confirmed.

The apparatus also includes an arrhythmiagraph which compresses pulse times (R–R intervals) into compact form seen as parallel vertical spikes, one for each beat and with a height proportional to pulse time. The resulting arrhythmiagram makes possible the

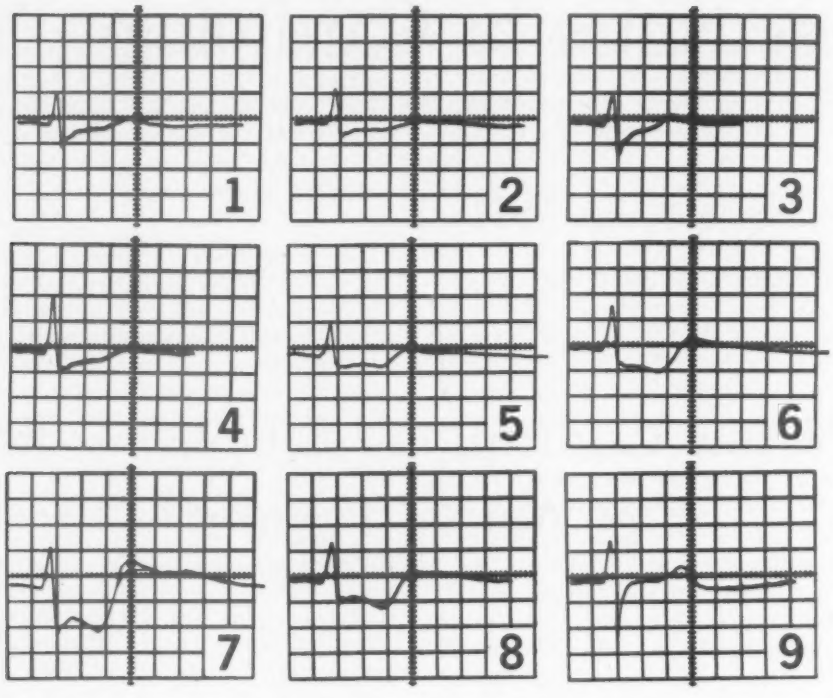


FIG. 1. Series of electrocardiograms photographed from the AVSEP screen during an anginal attack while the patient was lifting heavy boxes.

rapid quantitative counting of all premature systoles in a given number of hours, for example, thus allowing convenient study of factors increasing or decreasing such events.

Letters to the Editor

Muscular Subaortic Stenosis

Dear Editor:

On page 860 of Volume VII of the Journal there appears an article entitled "Muscular Subaortic Stenosis" by Drs. Daoud, Gallaher and Kaplan. I believe this article is worthy of some comment, because it seems to me to demonstrate what can happen when scientific medicine runs amuck.

You will note that in this case report the youngster was admitted for correction of a cyst of the eyelid. As a result of a heart murmur and a palpable liver the child wound up having a left heart catheterization. A pressure gradient was allegedly detected across the aortic valve. I would like to point out that left ventricular systolic pressure was only 105 mm. Hg, which corresponds very well with the auscultatory pressure in the arm taken at the time of admission. An examination of the pressure curves and Figure 3 in the article suggests very strongly that the aortic curve is badly damped. On the basis of the single physiologic measurement, apparently, he was subjected to open heart surgery and unfortunately did not survive the procedure. Surely, this was a rather disastrous outcome for hospitalization for an eyelid cyst!

It seems to me that the interpretation of data presented in this case, that this child had idiopathic ventricular hypertrophy without any significant outflow obstruction of the left ventricle but with a damped arterial pressure curve taken at the time of left heart catheterization, better fits the facts than the authors' interpretation that there was a significant obstruction at the level of the aortic valve. It seems to me that the presence of a low ventricular systolic pressure, in the face of what was presumed to be severe aortic stenosis, should have been examined with considerably more skepticism than evidently it was. Apparently, congestive heart failure was thought to be responsible for the low ventricular systolic pressure, but the only fact bearing on the presence of ventricular failure in this instance was the fact that the liver was palpable clinically. No mention is made under the autopsy findings regarding liver size or microscopic evidence of congestion. It seems to me that this relevant fact should have been reported along with the other data.

At least the authors have learned to be "cautious in such atypical cases, especially if surgery is contemplated." It is to be hoped that they also will be cautious in interpreting the accuracy of their physiologic data, and possibly it might be well if they would check the frequency response and damping characteristics of the catheter-manometer system used in their studies in infants.

GEORGE R. MOFFITT, JR., M.D.
Harrisburg, Pennsylvania

AUTHOR'S COMMENT

There was incontrovertible evidence of obstruction, particularly to the left ventricular outflow, in the child reported as having muscular subaortic stenosis. This was confirmed at autopsy. It is appreciated that the published pressure curves are damped. The purpose of the paper was to emphasize the difficulty of differentiating congenital aortic stenosis from obstructive lesions produced by cardiomyopathies. The indication for left heart catheterization and open heart surgery are stated clearly in the paper. They included a greatly enlarged heart, congestive heart failure and electrocardiographic evidence of marked left ventricular hypertrophy. At autopsy the liver was enlarged, weighed 370 gm. (normal 295 to 304 gm.) and showed evidence consistent with chronic congestion.

GEORGES DAOUD, M.D.
Cincinnati, Ohio

College News

PRESIDENT'S COLUMN

The Work Shops

SINCE ITS beginning, the College has offered an Annual Meeting and an Interim Meeting. These have been successful and there is good argument for continuing in just this pattern. However, the growth of the Work Shops has to a considerable extent lessened the reasons for the Interim Meeting. If the Work Shops continue to develop in the manner which seems possible, the members of the College will have the opportunity of visiting one or several medical centers each year and enrolling in specific programs developed according to the College's needs. These, when combined with the Annual Meeting, would offer a broad range of educational approaches and still maintain the opportunity for good fellowship . . . which must remain an essential obligation of the College.

The Work Shops have been a characteristic of the College since its beginning. Their intent has been to make available to the members the opportunity of visiting and working in laboratories of distinguished scientists and clinicians. As the concept has developed, it has become apparent that the Work Shops will take two directions: (1) Work Shops which are of a symposium nature and lend themselves to audiences of twenty-five to several hundred; and (2) Work Shops which are tutorial in design and will give a very small group, perhaps from two to ten persons, the privilege to come and work under the personal tutelage of a scientist or a clinician offering instruction and experience in a special discipline or skill. In this current year we will explore several approaches to extending the Work Shop concept; that which proves successful, we will develop. The College is youthful and able to experiment; lines of administration are short and flexible. Try to participate in at least one of the programs and be certain that you pass on to us your thoughts, criticisms and suggestions. The Work Shops have played a major role in the curriculum of the College and are a logical area for intensification of the College's effort.

E. GREY DIMOND, M.D.
President

First International Circuit Course

Cardiovascular Postgraduate Courses to be Presented in Manila and Taipei

THE AMERICAN COLLEGE OF CARDIOLOGY in collaboration with the United States Department of State will present cardiovascular symposia in the Philippines and Taiwan under the auspices of the Philippine Ministry of Health, the Philippine Medical Association, the Philippine Heart Association, the Philippine Federation of Private Medical Practitioners and the University of Santo Tomas. The sponsor in Taiwan will be the National Defense Medical Center.

The first faculty, under the leadership of Dr. E. Grey Dimond, is Dr. George Burch, Dr. Eliot Corday, Dr. Simon Dack and Dr. C. Walton Lillihei.

Dr. Mariano Alimurung, Governor for the American College of Cardiology for the Philippines, will be the Program Director. Dr. Alimurung visited in the United States in September to arrange for the details of the curriculum and the selection of the faculty. The Program Director in Taipei, Taiwan, will be Dr. Nong Ting, Professor and Chairman of the Department of Medicine, National Defense Medical Center.

The first symposium will be conducted in Manila, Philippines, October 26 to November 1; the second, in Taipei, Taiwan, on November 3 and 4, 1961.

The second and third International Circuit Courses in Cardiology are being developed for Lisbon, Portugal, and Istanbul, Turkey, in February 1962 and for Paris, France, and Jerusalem, Israel, in March 1962.

American College of Cardiology Workshop

November 17, 1961, University of Pennsylvania, Philadelphia, Pennsylvania

Coordinator: Hadley L. Conn, Jr., M.D.

Morning Session

Donnor Auditorium, Hospital of the University of Pennsylvania

9:15–11:30 a.m.

PANEL ON DIGITALIS

Chairman: T. G. SCHNABEL, JR., M.D., Assoc. Prof. of Medicine, University of Penn. School of Medicine

1. Cellular Aspects of Digitalis Action.
   ROBERT LUGHI, M.D., Assoc. in Medicine, University of Penn. School of Medicine
2. Present Views of Mechanisms of Digitalis Action.
   THEODORE RODMAN, M.D., V. A. Hospital, Philadelphia Inst. in Medicine, Temple University School of Medicine
3. Studies Relating to Cardiac Failure and the Therapeutic Indications for Digitalis Therapy.
   T. G. SCHNABEL, JR., M.D., Assoc. Prof. of Medicine, University of Penna. School of Medicine
4. Question–Answer Period
5. Recent Developments in the Mechanisms of Action and Clinical Use of Quinidine.
   HADLEY L. CONN, JR., M.D., Assoc. Prof. of Medicine, University of Penn. School of Medicine

Afternoon Session

Alumni Hall, Hospital of the University of Pennsylvania

1:00–4:15 p.m.

PRESENT STATUS OF TREATMENT OF AORTIC VALVULAR DISEASE

Chairman: HARRY F. ZINSSER, M.D., Assoc. Prof. of Medicine, University of Penn. School of Medicine

1. Newer Diagnostic Methods for Evaluating Aortic Valvular Lesions.
   JOHN HELWIG, M.D., Assoc. in Medicine, University of Penn. School of Medicine
2. Medical Management and Indications for Surgery of Aortic Valvular Lesions.
   HARRY F. ZINSSER, M.D., Assoc. Prof. of Medicine, University of Penn. School of Medicine
3. Review of Surgical Procedures Used in the Treatment of Aortic Valvular Lesions.
   WILLIAM F. BLAKEMORE, M.D., Assoc. Prof. of Surgery, University of Penn. School of Medicine
4. Total Prosthetic Replacement of the Diseased Aortic Valve.
   EARLE KAY, M.D., St. Vincents Charity Hospital, Cleveland, Ohio
5. Question–Answer Period

CARDIAC PACEMAKERS

Chairman: SAMUEL BELLET, M.D., Chief of Cardiology, Philadelphia General Hospital

1. Historical Development and Clinical Experience with Cardiac Pacemakers.
   PAUL M. ZOLL, M.D., Assoc. Prof. of Medicine, Harvard University School of Medicine, Boston, Mass.
2. Studies of the Effect of Pacemakers and Pacemaker Rate on Circulatory Dynamics.
   CLAUDE JOYNER, M.D., Asst. Prof. of Medicine, University of Penn. School of Medicine
3. The Future of Cardiac Pacemakers in Light of Recent Developments.
   SAMUEL BELLET, M.D., Chief of Cardiology, Philadelphia General Hospital
4. Question–Answer Period

AMERICAN COLLEGE OF CARDIOLOGY

CARDIOVASCULAR WORKSHOP

The Staff of the *Institute for CardioPulmonary Diseases* of the *Scripps Clinic and Research Foundation*, La Jolla, California, will offer a POST GRADUATE COURSE FOR PHYSICIANS on December 5, 6, 7, 8, 1961.

The Title of the Program is CARDIOLOGY: PHYSIOLOGY and BIOCHEMISTRY

Tuition is $50.00 for Members and Fellows of American College of Cardiology.
Tuition is $100.00 for other physicians. Residents and Internes admitted without charge.

Registration will be in the main lobby at 8:30 A.M., Tuesday, December 5, 1961, and instruction will begin at 9:00 A.M. The course will run four full days, 9:00 A.M. to 5:00 P.M. and two evening sessions, 7:00 to 9:00 P.M. Applications for enrollment accompanied by check should be sent to: Scripps Clinic and Research Foundation, 476 Prospect Street, La Jolla, California.

If you wish further information regarding lodging, please write: The La Jolla Town Counsel, Inc., 7923 Herschel Avenue, La Jolla, California.

The subjects to be covered are listed below. This will be an intensive program devoted to demonstrations of the practical developments in these fields and the presentations will be directed to the practicing physician.

Subjects:

1. Basic Principles of Electrocardiography
2. Spatial Electrocardiography and Vectorcardiography
3. Electrocardiogram in Congenital Heart Disease
4. Concepts of Systolic and Diastolic Overload
5. EKG Reading Session
6. Peri-infarction Block
7. Biochemistry of the Catecholamines
8. Biochemistry of Lipid Metabolism
9. A Consideration of Medical Thyroidectomy
10. New Concepts of Respiratory Control
11. Use of Indicator Dilution Studies in Cardiovascular Disease
12. Cine Angiocardiography
13. The Anatomy of Coronary Disease
14. The Biochemistry of Myocardial Metabolism
15. The Physiology of Angina
16. The Exercise Electrocardiogram
17. The Electrocardiogram and Vectorcardiogram in Acute Myocardial Infarction
18. Clotting Mechanisms in Ischemic Heart Disease
19. Great Vessel Disease, Pathology and Surgical Therapy
20. The Carcinoid Syndrome
21. Clinico-Pathological Conference
22. Biochemistry of Lipid Metabolism
23. Phonocardiography in Congenital Heart Disease
24. Phonocardiography in Acquired Heart Disease
25. Low Frequency Precordial Movements and other Reference Tracings
26. Case Presentations
27. Monitoring of Cardiovascular Events
28. Basilar Artery Insufficiency
29. Cine Renal Arteriograms
30. The Biochemistry of Cardiac Glycosides

Instructors: E. Grey Dimond, M.D.; Ivan Baronofsky, M.D.; Alberto Benchimol, M.D.; David B. Carmichael, M.D.; John C. Carson, M.D.; Herman F. Froeb, M.D.; Leslie H. Gaelen, M.D.; John J. Kelley, Jr., M.D.; William J. Kuzman, M.D.; Ernest E. Pund, Jr., M.D.; Robert Van Citters, M.D.; Willard P. Vanderlaan, M.D., Jacinto J. Vazquez, M.D.; Anton S. Yuskis, M.D.; Darrell D. Fanestil, M.D.; Byong Mok Kim, M.D.; James E. Lasry, M.D.; Bernard Leboeuf, M.D.; Robert E. Lee, M.D.; Jean F. Legler, M.D.; Harold M. Lowe, M.D.; Luis Morettin, M.D.; Mark W. Roberts, M.D.

PUBLISHER'S INFORMATION PAGE

The Editors and Publishers of **THE AMERICAN JOURNAL OF CARDIOLOGY** welcome concise articles on new findings in cardiology. As is customary in professional publications, statements in articles are the responsibility of the authors; articles must be contributed solely to **THE AMERICAN JOURNAL OF CARDIOLOGY**; material is copyrighted and may not be reproduced without permission of the publishers.

Preparation of Manuscripts

Authors are requested to follow these instructions carefully in preparing manuscripts: Please double space with good margins; type on one side of the sheet only; make a carbon copy for yourself and send the original with one carbon copy to the editorial office, 466 Lexington Avenue, New York 17, New York; include full name, degrees, staff position and affiliation; list bibliographic references in numerical order as referred to in text at the end of the article (not in footnotes). Please make certain each reference contains the name of author with initials; title of article; name of periodical with volume, page and year. For example: LEV, M. and ROWLATT, U. F. Pathology of mixed levocardia. A review of thirteen cases of atrial or ventricular inversion with or without corrected transposition. *Am. J. Cardiol.*, 8:216, 1961.

Preparation of Illustrations

So that your article will be presented most effectively, illustrations must be glossy prints or professional drawings in black ink (never in blue; it will not reproduce well). All printing on illustrations should be done professionally or with heavy type. Reference to all illustrations should be inserted in the text in consecutive order. Please follow these identification instructions: Write the figure number and the author's name on the back of each illustration and indicate the top.

Type legends for illustrations on a separate sheet with numbers corresponding to those on the photographs or drawings. Please do not attach legends to the pictures.

A reasonable number of illustrations are supplied free of cost; we know the authors will understand that special arrangements must be made with the publishers for excess illustrations and tables.

Reviews, Abstracts

Books for review may be sent directly to the Editor, Simon Dack, M.D., **The American Journal of Cardiology,** 466 Lexington Avenue, New York 17.

Permission to abstract must be obtained from the publisher. Only paid circulation journals will be permitted to abstract.

Reprints

Orders for reprints of articles should be sent directly to the Publisher, **The American Journal of Cardiology,** 466 Lexington Avenue, New York 17, New York. Prices are quoted after articles are published.

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SCOPE — A formal presentation, 10 minutes in length, describing original investigation in which the contestant did either the work or was a significant member of investigating team.

PROCEDURE — An original manuscript and letter indicating intention to enter the competition must be in hands of Executive Director by *January 1, 1962.*

An *accompanying* letter from the chief of the service or laboratory indicating his willingness to have the material presented in the competition.

Judging to be made by the Committee of Judges selected by the President of the American College of Cardiology and their decision to be based upon (a) excellence and originality of investigation (b) excellence of written manuscript (c) excellence of presentation.

Competition to be in Denver, Colorado, upon the occasion of the 11th Annual Meeting of the American College of Cardiology, date May 29 to June 2, 1962.

Address queries and manuscript to: Executive Director, American College of Cardiology, Empire State Building, 350 Fifth Avenue, New York 1, New York.



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*Build and Blood Pressure Study, Society of Actuaries, Chicago, Ill., 1959, vol. 1, pp. 84, 89, 92. Trademark: TEN-TAB T-3479/60-1

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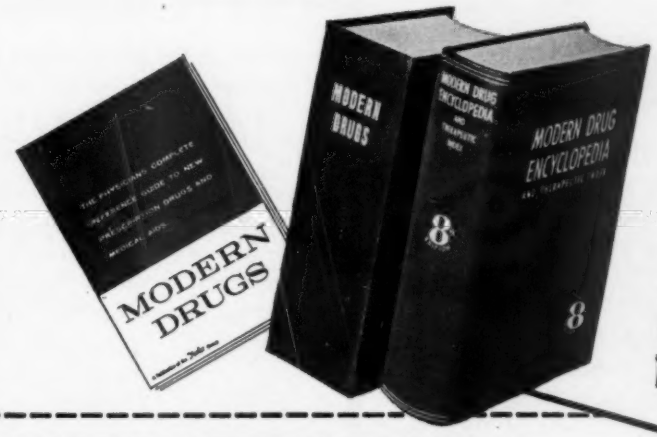
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after 3 years' clinical experience:
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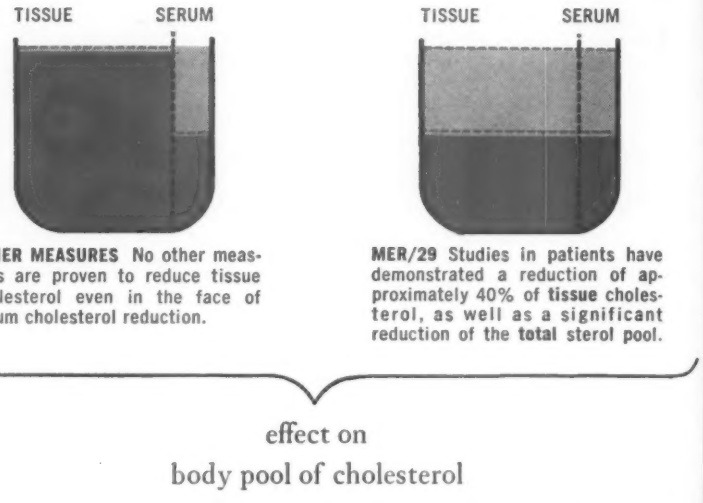
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effect on
body pool of cholesterol

WE KNOW THE BENEFITS OF MER/29

We know that, in some patients, concurrent clinical benefits attend the use of MER/29. Published papers on MER/29 therapy to date report improvement in 50 of the 79 anginal patients reported in these studies, and comparable results are being obtained in similar studies now in progress. Among the other benefits reported are:

decreased incidence and severity of anginal attacks

improved* ECG *patterns

diminished nitroglycerin dependence

increased sense of well-being

"During triparanol [MER/29] therapy there was a definite improvement in the electrocardiographic tracings in response to exercise in 3 of 11 subjects with angina pectoris." —*Hollander, W.,* et al.: *J.A.M.A.* 174:*5 (Sept. 3) 1960.*

"Nitroglycerine requirements decreased in 3 [of 5 outpatient] patients, including the patient showing electrocardiographic improvement....Three [of 4 private male patients], after a lapse of some weeks, showed improvement in exercise electrocardiograms, which was sustained but not further improved in subsequent observations." —*Corcoran, A. C.,* et al.: *Progr. Cardiovasc. Dis.* 2: *(Pt.1) 576 (May) 1960.*

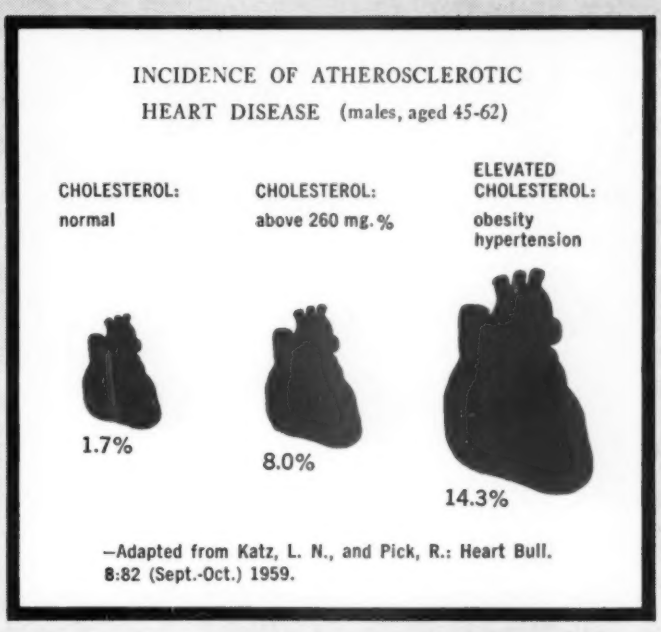
"Of the 45 patients with coronary artery disease followed for 1 year, 16 had a history of frequent anginal attacks. Fourteen of these spontaneously stated that their angina disappeared within 2 months of [MER/29] therapy....In one patient...with persistent coronary insufficiency pattern (ST segment depressions in multiple leads), there was a complete reversion to a normal tracing during MER/29 therapy with associated clinical improvement in angina." —*Lisan, P.: Progr. Cardiovasc. Dis.* 2: *(Pt. 1) 618 (May) 1960.*

. . . . what we are learning about atherosclerosis

WHY MER/29 MAY FAVORABLY ALTER ATHEROSCLEROSIS

"It has become generally accepted that elevated blood cholesterol or lipid, if sustained long enough, leads to early atherosclerosis."
–Page, I. H.: Mod. Med. 29:71 (Mar. 20) 1961.

Epidemiologic studies show that low cholesterol levels are associated with low incidence of atherosclerosis and coronary artery disease. On the basis of such studies, Stamler has said: "...a 15 to 20 per cent reduction in mean serum cholesterol levels alone might be associated with a 25 to 50 per cent reduction in coronary disease incidence rates in middle-aged men."
–Stamler, J.: Am. J. Pub. Health 50:(Pt. 2) 14 (Mar.) 1960.



THE DECISION FACING THE PHYSICIAN

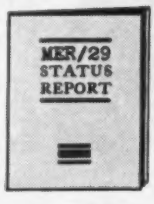
Despite our knowledge of the action, benefits and safety of MER/29, much remains to be discovered about the basic concept of cholesterol-lowering therapy. In this, MER/29 is comparable to the well-accepted use of antihypertensive agents: we know they lower blood pressure, but we cannot prove that lowering blood pressure will also lower morbidity or mortality. Yet few physicians hesitate to use these agents. The possible good is too great to ignore.

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1. Biegeleisen, H. I.: Clin. Med. *2*:1005, 1955. 2. Roberts, J. T.: Clin. Med. *4*:1375, 1957. 3. Kamil, M., and Klinger, I.: New York State J. Med. *59*:3398, 1959.

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references: (1) Hirshleifer, L.: Adjunctive therapy in cardiacs, presented at the Spring Scientific Symposium, Connecticut Acad. Gen. Pract., Hartford, Conn., March 16, 1961. (2) Fronman, I. P.: The Alleviation of Stress in the Elderly Cardiac Patient, **ibid.** (3) Kent, E. A.: Management of the Hyperactive Geriatric Patient, **ibid.**

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References: 1. Albert, A.: Isosorbide Dinitrate in Treatment of Angina Pectoris, Journal Lancet 81:112 (Mar.) 1961. 2. Shapiro, S.: Angina Pectoris: Treatment with Isosorbide Dinitrate, Angiology 12:53 (Feb.) 1961. 3. Leslie, R. E.: Coronary Vasodilators—A Comparative Study, Western Medicine 2:56 (Feb.) 1961. 4. Russek, H. I.: Comparative Responses to Various Nitrates in the Treatment of Angina Pectoris, Journal of the Kansas City Southwest Clinical Society 36:14 (Dec.) 1960. 5. Berry, J. W.; Carney, R. and Lankford, H.: Clinical Experiences with Isosorbide Dinitrate (Isordil®), Angiology 12:254 (June) 1961. 6. Sherber, D. A. and Gelb, I. J.: The Clinical Pharmacology of Isosorbide Dinitrate: A Unique, New Nitrated Polyalcohol, ibid. 7. Joseph, L. G. and Mancini, A.: Isosorbide Dinitrate in Angina Pectoris, ibid.

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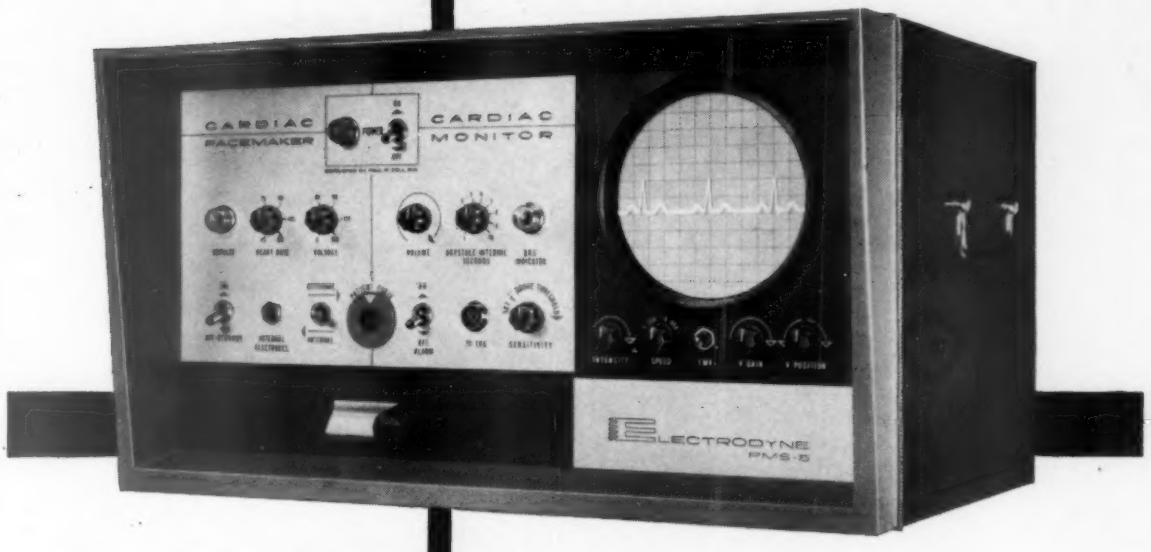
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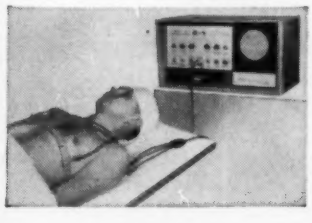
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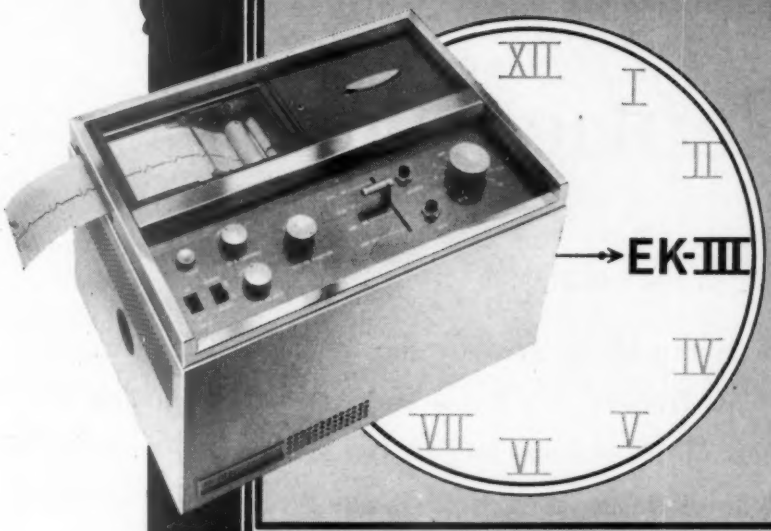
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1. Youmans, J. B.: Am. J. Med. 25:659 (Nov.) 1958.
2. Kampmeier, R. H.: Am. J. Med. 25:662 (Nov.) 1958.

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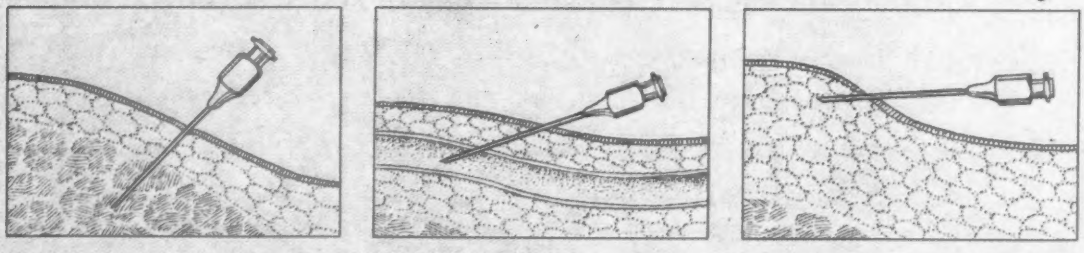
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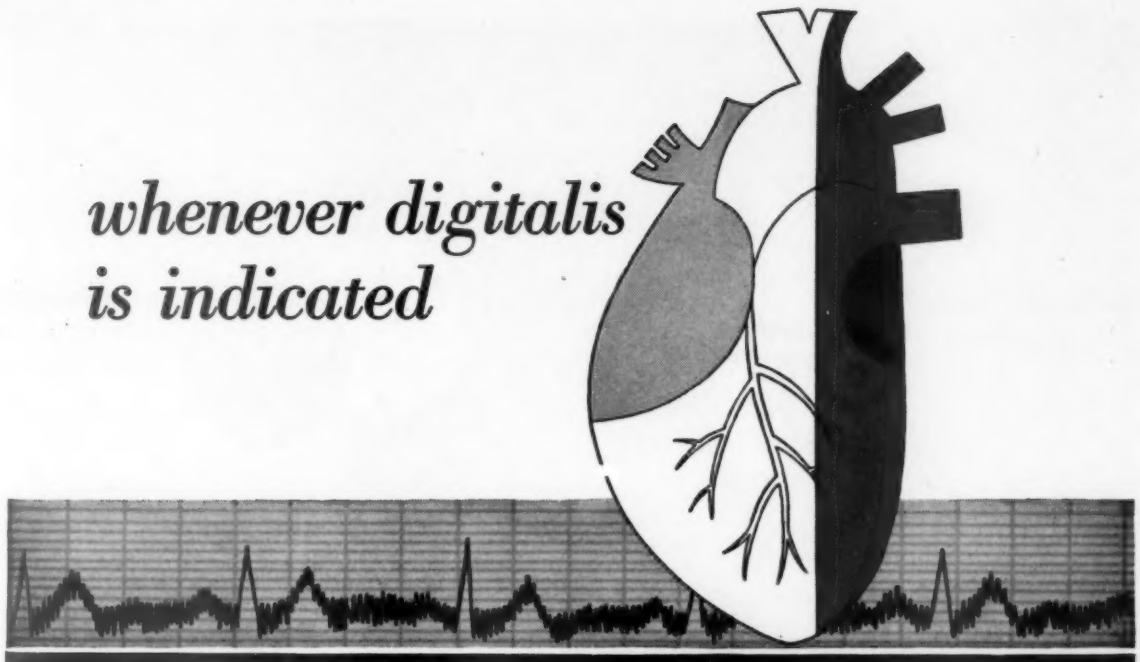
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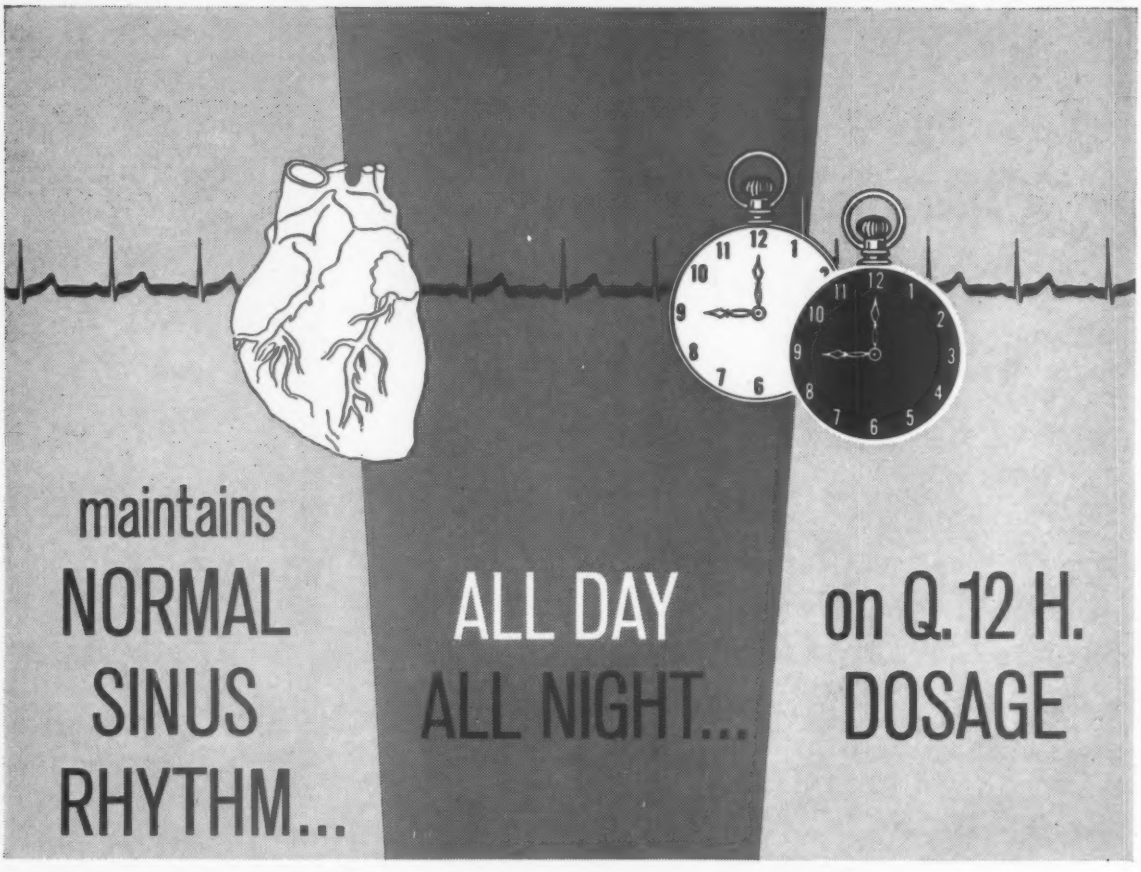
Lown, B., and Levine, S. A.: Current Concepts in Digitalis Therapy, Boston, Little, Brown & Company, 1954, p. 23, par. 2.

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1. Manchester, B.: Ann. Int. Med. *47*:1202 (Dec.) 1957. 2. Harper, B.F., and Johnson, R.: J.M.A. Georgia *45*:149 (April) 1956. 3. Wood, J.L. *et al.*: J.A.M.A. *159*:635 (Oct.) 1955. 4. Sise, H. *et al.*: Am. Heart J. *53*:132 (Jan.) 1957. 5. Dewar, H.A.: Practitioner *186*:41 (Jan.) 1961.

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For further information on the limitations, administration, and prescribing of EQUANITRATE, see descriptive literature or current direction circular.

†Russek, H.I.: Am J. Cardiol. *3*:547 (April) 1959.

Supplied: EQUANITRATE 10 (200 mg. meprobamate, 10 mg. pentaerythritol tetranitrate), white oval tablets, vials of 50. EQUANITRATE 20 (200 mg. meprobamate, 20 mg. pentaerythritol tetranitrate), yellow oval tablets, vials of 50.

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Fuller, H. L.: Angiology *11*:200 (June) 1960.

Simple and safe for long-term therapy, Clarin* (sublingual heparin) effectively controls the prolonged postprandial lipemia associated with atherosclerosis by facilitating the normal physiologic breakdown of fats. Unlike parenteral heparin, the use of Clarin requires no clotting-time or prothrombin determinations. The antilipemic activity of each manufactured lot of tablets is confirmed by sublingual control tests in animals.

Indication: For the management of hyperlipemia associated with atherosclerosis, especially in the postcoronary patient. *Dosage:* After each meal, hold one tablet under the tongue until dissolved. *Supplied:* Bottles of 50 pink, sublingual tablets, each containing 1500 I.U. heparin potassium.

An informative booklet, "Hyperlipemia, Heparin and Management of the Postcoronary Patient," is available from Thos. Leeming & Co., Inc., 155 East 44th St., New York 17, N. Y.

*Registered trade mark. Patent applied for.

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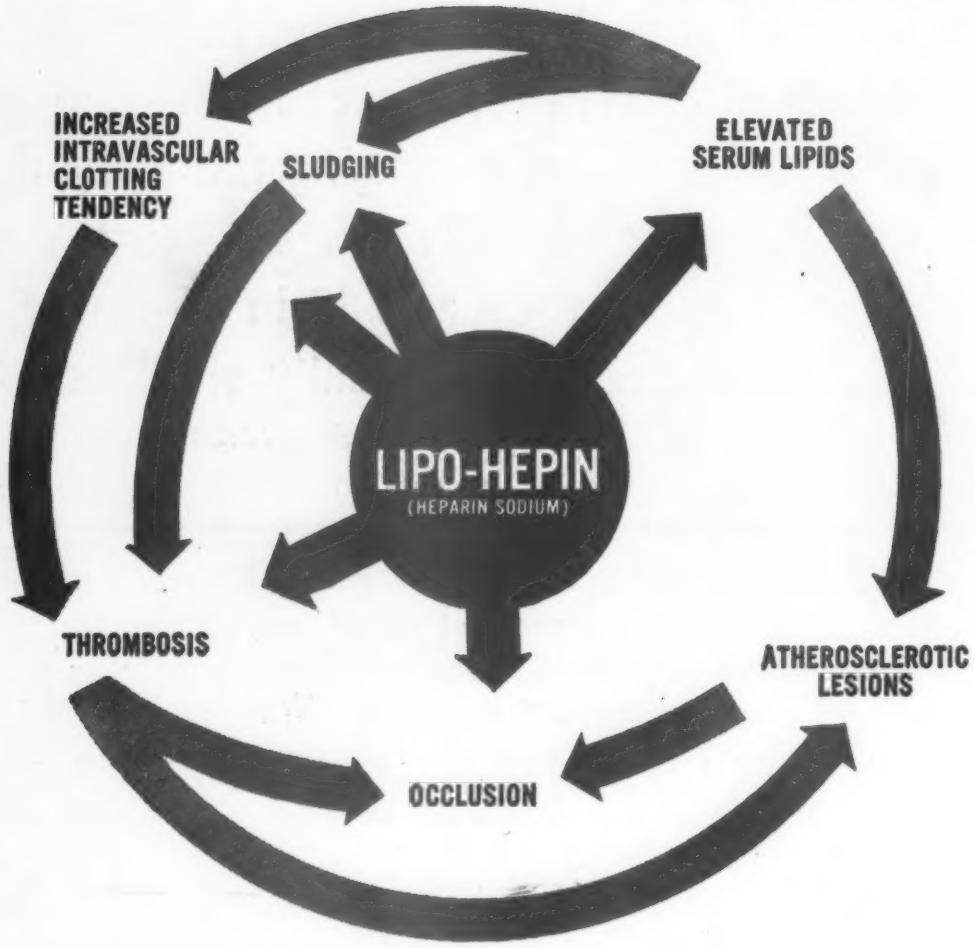
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